

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS AND COUNTER-  
DESIGNATIONS FOR MICHAEL MEYER, Ph.D.**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached corrected deposition designations and counter-designations for the January 23, 2007 deposition of Michael Meyer, Ph.D., Senior Project Leader of the Discovery Program (ABT-594).

Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By:     /s/ Eric J. Lorenzini      
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**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008

\_\_\_\_\_  
/s/ Ozge Guzelsu

## Michael Meyer Deposition Designations

<b>Depo Date</b>	<b>Witness</b>	<b>Hancock Designation</b>	<b>Abbott Counter Designation</b>	<b>Abbott Designation</b>	<b>Deposition Exhibit</b>	<b>Plaintiff Exhibit</b>	<b>Defendant Exhibit</b>
1/23/2007	Meyer, Michael	5:1-5:9					
1/23/2007	Meyer, Michael	6:3-6:8					
1/23/2007	Meyer, Michael	6:18-11:11					
1/23/2007	Meyer, Michael	11:18-13:8					
1/23/2007	Meyer, Michael	13:19-17:8					
1/23/2007	Meyer, Michael	21:14-23:3					
1/23/2007	Meyer, Michael	23:16-23:19	23:8-23:15; 23:20-24:3				
1/23/2007	Meyer, Michael	27:12-28:10					
1/23/2007	Meyer, Michael	41:12-41:19					
1/23/2007	Meyer, Michael	41:22-43:3			1	BR	
1/23/2007	Meyer, Michael	45:9-47:7	47:8-47:20		1	BR	
1/23/2007	Meyer, Michael			48:7-49:6			
1/23/2007	Meyer, Michael	49:22-51:18	47:8-47:20				
1/23/2007	Meyer, Michael	53:10-53:24					
1/23/2007	Meyer, Michael	55:6-56:19			3	BU	
1/23/2007	Meyer, Michael			56:20-57:13			
1/23/2007	Meyer, Michael			59:3-60:16			



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1/23/2007	Meyer, Michael	64:10-65:5	64:1-64:9				
1/23/2007	Meyer, Michael	64:10-65:5	65:6-66:19				
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1/23/2007	Meyer, Michael			95:6-95:16			
1/23/2007	Meyer, Michael			98:7-100:3			
1/23/2007	Meyer, Michael			107:19-108:23			
1/23/2007	Meyer, Michael			109:21-110:8			
1/23/2007	Meyer, Michael			111:6-111:24			
1/23/2007	Meyer, Michael			113:7-113:16			
1/23/2007	Meyer, Michael			114:20-115:13			
1/23/2007	Meyer, Michael	117:11-118:10			12	EN	
1/23/2007	Meyer, Michael	122:22-123:10	122:3-122:21				
1/23/2007	Meyer, Michael		123:11-124:15		12	EN	
1/23/2007	Meyer, Michael	124:18-126:17			13	EP	
1/23/2007	Meyer, Michael			129:9-130:24			
1/23/2007	Meyer, Michael			134:7-135:24			

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1/23/2007	Meyer, Michael			144:16-144:24			
1/23/2007	Meyer, Michael	147:10-147:15			16	EV	
1/23/2007	Meyer, Michael			147:17-148:20			
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1/23/2007	Meyer, Michael	155:15-157:19	153:21-155:13				
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1/23/2007	Meyer, Michael	162:1-163:1					
1/23/2007	Meyer, Michael			167:5-168:18			
1/23/2007	Meyer, Michael			171:8-179:9			
1/23/2007	Meyer, Michael			180:19-181:8			
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1/23/2007	Meyer, Michael	185:15-186:24					
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1/23/2007	Meyer, Michael	213:9-215:3					
1/23/2007	Meyer, Michael			216:22- 217:19			
1/23/2007	Meyer, Michael	218:2-219:20			29	DM	
1/23/2007	Meyer, Michael	220:16-224:12			29	DM	

## **Color Key to Deposition Designations**

 **Designation by Plaintiffs**

 **Counter Designation by Defendants**

 **Designation by Defendants**

Meyer, Michael David (Linked) 1/23/2007 9:01:00 AM

1 UNITED STATES DISTRICT COURT  
2 FOR THE DISTRICT OF MASSACHUSETTS

3  
4 JOHN HANCOCK LIFE INSURANCE )  
5 COMPANY, JOHN HANCOCK VARIABLE )  
6 LIFE INSURANCE COMPANY and )  
7 MANULIFE INSURANCE COMPANY )  
8 (f/k/a INVESTORS PARTNER )  
9 INSURANCE COMPANY), )

10 Plaintiffs, ) Civil Action No.  
11 -vs- ) 05-11150-DPW

12 ABBOTT LABORATORIES, )  
13 Defendant. )

14  
15  
16 THE VIDEOTAPED DEPOSITION OF

17  
18 MICHAEL DAVID MEYER

19  
20 January 23, 2007

21  
22  
23  
24

1 (WHEREUPON, the witness was duly  
2 sworn.)

3 MICHAEL DAVID MEYER,  
4 called as a witness herein, having been first duly  
5 sworn, was examined and testified as follows:

6 EXAMINATION

7 BY MR. DAVIS:

8 Q. Good morning, Dr. Meyer.

9 A. Good morning.

10 Q. And my name is Brian Davis. I'm going  
11 to be asking you a series of questions here today.  
12 If at any point in time you don't understand any of  
13 my question, please just say so and I will try to  
14 give you a clear question. Is that fair?

15 A. Okay.

16 Q. In addition, as we go through the  
17 deposition, you will need to verbalize your  
18 responses. The Court Reporter cannot record head  
19 shakes or the like. Do you understand that?

20 A. Yes.

21 Q. And if at any point in time you'd like  
22 to take a break, please me know and I'll try to  
23 accommodate you as soon as I can after that. This  
24 is not intended to be a torture test. Do you

1 understand that?

2 A. Right. Thank you.

3 Q. Dr. Meyer, where do you work?

4 A. I work for Abbott Laboratories in Abbott  
5 Park, Illinois.

6 Q. And would you state your full name for  
7 the record, please.

8 A. Michael David Meyer.

9 MR. DAVIS: Özge, by the way, same  
10 stipulations that we've been operating under.

11 MS. GÜZELSU: Yes, and there is no need for a  
12 notarization for the deposition transcript.

13 MR. DAVIS: Correct, if he just signs under  
14 the pain and penalties of perjury within 30 days,  
15 that will be acceptable.

16 MS. GÜZELSU: Okay. Great. Thank you.

17 BY MR. DAVIS:

18 Q. What is your home address?

19 A. 25151 Amanda Court, Lake Villa,  
20 Illinois.

21 Q. Do you have any plans to move from that  
22 address any time soon?

23 A. No.

24 Q. You said you work for Abbott?

1 A. That's correct.

2 Q. What's your current position?

3 A. I'm a senior project leader.

4 Q. Senior project leader?

5 A. Yes.

6 Q. How long have you been a senior project

7 leader?

8 A. About five years.

9 Q. And what does a senior project leader

10 do?

11 A. I'm responsible for managing a project

12 within our Discovery organization.

13 Q. And what is the Discovery organization?

14 A. The Discovery organization is the part

15 of our research and development organization that's

16 responsible for identification of new molecules for

17 development.

18 Q. You work in the pharmaceutical side of

19 Abbott's business?

20 A. That's correct.

21 Q. And in Discovery, part of what you're

22 doing is trying to identify new molecules or

23 compounds that could potentially be developed into

24 pharmaceutical compounds?



1 A. That is correct.

2 Q. Drugs.

3 When did you first go to work for

4 Abbott?

5 A. In July 1984.

6 Q. Have you worked for Abbott consistently

7 since that time?

8 A. Yes.

9 Q. In a variety of positions?

10 A. Yes.

11 Q. Let's just go back briefly. What is

12 your educational background, please?

13 A. I have a Bachelor of Science Degree from

14 Dickinson College and a Ph.D. from Penn State

15 University.

16 Q. In what field is your Ph.D.?

17 A. Organic chemistry.

18 Q. When did you receive your Ph.D.?

19 A. 1980.

20 Q. Did you work somewhere other than Abbott

21 before -- strike that.

22 Where did you work between 1980 and

23 1984?

24 A. From 1980 to 1982 I worked for Mayo

1 Clinic in Rochester, Minnesota. And from 1982 to  
2 1984 I worked for SmithKline and French, a  
3 pharmaceutical company, in Philadelphia,  
4 Pennsylvania.

5 Q. And, briefly, what positions have you  
6 held at Abbott since you've joined Abbott in 1984?

7 A. When I was hired I was a research  
8 chemist and was promoted to senior research  
9 chemist, research investigator, group leader,  
10 senior group leader, project leader, senior project  
11 leader.

12 Q. Have you always been in the Discovery  
13 side of the business?

14 A. Yes, I have.

15 Q. When you say you act as a senior project  
16 leader, do you work on different projects over time  
17 or is it always the same project?

18 A. I have worked on different projects over  
19 time.

20 Q. And typically how long do the projects  
21 last?

22 A. It's variable. From the time I became a  
23 project leader I worked on the nicotinic program  
24 for -- let's see, from 1998 until 2003, and then I

1 changed to a different program and I'm working on  
2 that project now.

3 Q. Do you typically work on more than one  
4 program at a time?

5 A. Typically no.

6 Q. You made reference to the nicotinic  
7 program. Is that also known as the nicotinic  
8 neuronal receptor program?

9 A. Yes.

10 Q. Or the NNR program?

11 A. Yes.

12 Q. If I have it correctly, you said you  
13 worked on that program from approximately 1998  
14 through 2003?

15 A. Yes.

16 Q. What positions did you hold with respect  
17 to that program?

18 A. In 1998 I was project leader and was  
19 promoted to senior project leader. I don't recall  
20 the exact date. But it was during that period. I  
21 think it was probably around 2001 or '2.

22 Q. Who did you -- who did you report to as  
23 project leader on the NNR program?

24 A. In 1998 I was reporting to Dr. Mike

1 Williams, and I cannot remember when Dr. Williams  
2 left Abbott and at which point I started to report  
3 to Dr. Jim Sullivan.

4 Q. And during the remainder of your  
5 involvement in the NNR program, did you report to  
6 Dr. Sullivan?

7 A. Yes.

8 Q. And when I refer to the NNR program you  
9 understand I'm referring to that nicotinic program,  
10 correct?

11 A. Yes.

12 Q. Have you worked on more than one  
13 nicotinic program while you've been employed at  
14 Abbott?

15 A. I don't understand what you mean by  
16 that.

17 Q. Let's go back for a moment.

18 Can you describe for me briefly what was  
19 or is the NNR program?

20 A. The basis of the program is -- it's  
21 based on a specific biologic target, which are  
22 neuronal nicotinic receptors. The focus of the  
23 program was to develop drugs that selectively  
24 interacted with various subtypes of the nicotinic

1 receptor family. So...

2 Q. So, it was to find -- if I have it

3 correctly, the NNR program was intended to identify

4 nicotinic compounds that might be useful for

5 development into pharmaceuticals, is that right?

6 A. Yes.

7 Q. And all the compounds that you were

8 looking at in the NNR project were all related in

9 some way in that they all acted or were thought to

10 act on nicotinic receptors in the brain?

11 A. That's correct.

12 Q. ABT-594 was an NNR, nicotinic neuronal

13 receptor, compound?

14 A. Yes.

15 Q. Was that one of the compounds that you

16 worked on in the course of the NNR project?

17 A. ABT-594 was discovered and approved for

18 development prior to the time when I joined the

19 program as project leader.

20 Q. So that drug, if it's fair to say, that

21 drug already had been discovered before you began

22 work on the NNR program?

23 A. That's correct.

24 Q. Did the NNR program exist before 1998?

1 A. Yes.

2 Q. So, you came into the program while it

3 was already underway?

4 A. That's correct.

5 Q. Do you know when the NNR program at

6 Abbott first began?

7 A. To the best of my knowledge I think it

8 was around 1990, but I'm not positive about that.

9 Q. Who did you take over for as project

10 leader of that program?

11 A. Dr. Steve Arneric.

12 Q. How do you spell the last name?

13 A. A-r-n-e-r-i-c.

14 Q. Did he leave Abbott at that time?

15 A. Not immediately.

16 Q. So, he was promoted or moved into a

17 different position?

18 A. That's correct.

19 Q. Now, at the time that you joined the NNR

20 program, was one of the focuses of the program to

21 find a backup for ABT-594?

22 A. That's correct.

23 Q. What is -- what is a backup?

24 A. During the course of a Discovery

1 program, we seek to find molecules that have  
2 similar profiles but addressing specific  
3 shortcomings of existing molecules.

4 Q. At the time that you joined the NNR  
5 program in '98, was it perceived or did you  
6 perceive that ABT-594 had specific drawbacks?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. Can you clarify that in terms of do you  
10 mean clinically or pre-clinically?

11 BY MR. DAVIS:

12 Q. Well, at the time that you were working  
13 on the NNR program to find a backup for ABT-594,  
14 did you understand that there were certain  
15 deficiencies or characteristics of ABT-594 that  
16 were deemed undesirable, unacceptable?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. Our understanding of the molecule was  
20 that from a preclinical perspective it had a  
21 therapeutic index that we could calculate based on  
22 preclinical models, and our goal was to identify  
23 molecules that had a larger therapeutic index.

24 We didn't know at that point whether the

1 therapeutic index that we understood from our  
2 preclinical experiments was going to correlate to a  
3 similar or less favorable or more favorable  
4 preclinical -- or therapeutic index clinically.

5 Q. Was one of the goals of the NNR program  
6 to find backups for ABT-594 that did not exhibit,  
7 at least to the same degree, side effects  
8 associated with ABT-594?

9 MS. GÜZELSU: Objection.

10 BY THE WITNESS:

11 A. A focus of the program was to identify  
12 molecules that had superior profile to ABT-594  
13 relative to -- my responsibility was relative to  
14 the preclinical profile of the compound.

15 BY MR. DAVIS:

16 Q. And when you say the "profile of the  
17 compound," profile would include things such as  
18 tolerability of the compound?

19 A. It would include -- specifically it  
20 would include the activity of the compound at  
21 the -- for the target indication relative to the  
22 activity of the compound to produce side effects in  
23 our animal models.

24 Q. There is no mystery here. I mean, at



1 the end of the day part of what Abbott was trying  
2 to do and part of what you were trying to do in the  
3 NNR program was identify NNR compounds that would  
4 be efficacious, correct?

5 A. Yes.

6 MS. GÜZELSU: Objection.

7 BY MR. DAVIS:

8 Q. That you hoped would have as good as --  
9 as good as or better therapeutic window than  
10 ABT-594, is that right?

11 A. Yes.

12 Q. One of the -- another goal was to try to  
13 find compounds that were as good or better than  
14 ABT-594 in terms of therapeutic window that also  
15 had better profiles --

16 MS. GÜZELSU: Objection.

17 BY MR. DAVIS:

18 Q. -- in terms of safety or tolerability,  
19 is that fair to say?

20 MS. GÜZELSU: Objection.

21 BY THE WITNESS:

22 A. Could you repeat the question, please.

23 BY MR. DAVIS:

24 Q. Sure. Part of what you were doing in

1 the NNR program was to identify compounds that were  
2 not only as efficacious as ABT-594 or more  
3 efficacious than ABT-594, you were trying to find  
4 backup compounds that had better profiles in terms  
5 of safety or tolerability, is that right?

6 MS. GÜZELSU: Objection.

7 BY THE WITNESS:

8 A. Yes.

9 BY MR. DAVIS:

10 Q. You mentioned that the NNR program --  
11 you worked on the NNR program through 2003?

12 A. I can't remember the exact date when I  
13 changed my current program and no longer had  
14 primary responsibilities for the NNR program, but  
15 it was about 2003.

16 Q. Did you remain in -- well, strike that.

17 Did the NNR program continue on after  
18 you no longer had primary responsibility for it?

19 A. Yes.

20 Q. Is it still in operation at Abbott, to  
21 your knowledge?

22 A. Yes.

23 Q. Who is currently the project leader or  
24 senior project leader for the NNR program?

1 Q. Have you made those available to counsel  
2 for production in this case?

3 A. I have.

4 Q. And, to your knowledge, are you aware of  
5 any documents at Abbott pertaining to the NNR  
6 program that have not been made available --

7 MS. GÜZELSU: Objection.

8 BY MR. DAVIS:

9 Q. -- to Abbott's counsel for production in  
10 this case?

11 A. To the best of my knowledge I have  
12 turned over all documents that are in my possession  
13 relating to this case. Relating to ABT-594.

14 Q. Did you have any involvement in the  
15 development of ABT-594?

16 A. I attended numerous meetings with the  
17 development team. I didn't have any  
18 decision-making responsibilities with that team.

19 Q. There was a development team for ABT-594  
20 at some point in time?

21 A. Yes.

22 Q. Who was on that development team, as  
23 best you recall?

24 A. This was a -- this was a large team.

1 I -- let me see. Dr. Chris Silber I believe headed  
2 the team at that point. Dr. Bruce McCarthy,  
3 Dr. Rita Driscoll, Jim Thomas was on the team.

4 Many, many people. Offhand I just can't  
5 produce a list of who all those people might be.

6 Q. Is -- is it consistent with your  
7 recollection that the development team was a  
8 cross-disciplinary team?

9 A. There were representatives from multiple  
10 disciplines, yes.

11 Q. For example, there were marketing  
12 representatives on the development team, is that  
13 right?

14 A. I'm -- I'm not exactly certain of what  
15 the role of people from the commercial part of the  
16 organization was. There were people from the  
17 commercial part of the organization.

18 Q. For example, Ms. Landsberg, do you know  
19 Ms. Landsberg, Andrea Landsberg?

20 A. Andrea Landsberg, yes. She was  
21 involved.

22 Q. Was she a member of the development  
23 team?

24 A. Well, she was -- I don't know exactly

1 what her responsibilities were. I know that she  
2 was on occasion at meetings that I attended  
3 relative to the development.

4 Q. When did you first -- strike that.

5 Were you a member first of the  
6 development team?

7 A. I guess I was.

8 Q. You didn't get a ring or a card or  
9 anything like that that you recall?

10 Did you -- were there regular meetings  
11 of the development team, to your knowledge?

12 A. Yes.

13 Q. And did you typically attend the  
14 meetings of the development team?

15 A. I attended many of them.

16 Q. How frequently did the ABT-594  
17 development team meet?

18 A. I think generally there were monthly  
19 meetings.

20 Q. Approximately what period of time do you  
21 recall the -- over what period of time do you  
22 recall the ABT-594 development team meeting?

23 A. I started attending meetings for the  
24 development team as soon as I took over my -- my

1 responsibilities as project leader for the  
2 nicotinic program. So, that was in midyear 1998.  
3 I think that's right.

4 Q. And approximately -- would have  
5 development team meetings for ABT-594 ceased, to  
6 your knowledge?

7 A. To my knowledge there are not ABT-594  
8 development team meetings at this point.

9 Q. When did they -- when did they stop, as  
10 best you recall?

11 A. I'm guessing somewhere around 2002 or  
12 2003. I can't remember exactly.

13 Q. How did you get notice of when the  
14 meetings were going to occur?

15 A. Meeting announcements would be sent  
16 through our Lotus Notes calendaring.

17 Q. Who typically chaired the meetings of  
18 the ABT-594 development team?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. There was -- there was an operations  
22 manager who had many of the responsibilities for  
23 the, you know, administrative tasks of setting up  
24 meetings and so forth and would set up agendas and

1 A. Some of our responsibilities dealt with  
2 more strictly scientific endeavors of mechanistic  
3 studies into how NNRs worked in various disease  
4 states.

5 Q. Is the -- is a backup the same thing as  
6 a follow-on?

7 A. To my way of thinking. I don't know  
8 what the exact distinction might be.

9 Q. So, to your thinking they are  
10 synonymous?

11 A. Yes.

12 Q. Does Abbott currently have any NNR  
13 compounds under development?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. Yes.

17 BY MR. DAVIS:

18 Q. What are they?

19 A. ABT-894, ABT-089, ABT-107, and there is  
20 a new one that I can't recall the ABT number.

21 Q. Again, these are all compounds that are  
22 out of Discovery and into actual development, is  
23 that right?

24 A. 894 and 089 are in development. ABT-107

1 is undergoing its final preclinical studies to  
2 ready it for first in human studies that are  
3 anticipated to occur within the next several  
4 months.

5 Q. Where is -- strike that.

6 What is the status of the development of  
7 ABT-894 currently?

8 MS. GÜZELSU: Objection.

9 BY THE WITNESS:

10 A. ABT-894 is currently in Phase I.

11 BY MR. DAVIS:

12 Q. Has Phase I testing ended?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. Well, that's -- that's hard to say.  
16 Frequently Phase I and Phase II will be occurring  
17 concurrently and then it's not always a break that  
18 when you start Phase II, Phase I has ended. There  
19 will be Phase I trials that will continue if -- if  
20 the development of ABT-894 continues into Phase II  
21 and Phase III, there still would likely be Phase I  
22 trials that would be continuing.

23 BY MR. DAVIS:

24 Q. Have any -- have any Phase I trials for



1 compound?

2 A. It is in Phase II.

3 Q. For what indications?

4 MS. GÜZELSU: Objection.

5 BY MR. DAVIS:

6 Q. If you know.

7 A. Cognition, attention deficit.

8 Q. Anything else?

9 A. According to the -- my understanding of

10 the development plan, it will be evaluated in

11 Alzheimer's disease as well.

12 Q. ABT-894, you said that's in Phase I,

13 perhaps moving into Phase II?

14 A. Yes.

15 Q. For what indications?

16 A. Neuropathic pain and cognition.

17 Q. ABT-594 also was under development for

18 neuropathic pain, is that right?

19 A. Yes.

20 MR. DAVIS: Let's mark this, please, as the

21 first exhibit.

22 (WHEREUPON, a certain document was

23 marked Meyer Deposition Exhibit

24 No. 1, for identification, as of

1 01-23-2007.)

2 BY MR. DAVIS:

3 Q. Dr. Meyer, I show you what's been marked

4 as Exhibit 1 at your deposition, ask you just to

5 take a few moments, look at the document and then

6 tell me if you've seen it before.

7 A. Yes, I believe I have seen it.

8 Q. This appears to be a summary of an

9 Analgesia Venture Portfolio Review that took place

10 in January of 1999. Do you see that?

11 A. I see that, yes.

12 Q. Did you attend this meeting?

13 A. I think I did. I'm not 100 percent

14 positive.

15 Q. There is a reference to you on the third

16 page of the document. It says that in the course

17 of the meeting you reviewed the Discovery strategy

18 and assumptions for future compounds. Do you see

19 that?

20 A. Yes.

21 Q. Do you recall doing that?

22 MS. GÜZELSU: Objection.

23 BY THE WITNESS:

24 A. There were many meetings that I made

1 those types of presentations that I -- I can't  
2 specifically assign that I did, but the indication  
3 would be that I did, yes.

4 Q. The analgesia venture, was that  
5 something different than the ABT-594 development  
6 committee or team?

7 A. My understanding is that they're one and  
8 the same.

9 Q. For the ABT-594 development team  
10 meetings that you attended, did you typically see  
11 minutes of the meetings after the meetings  
12 occurred?

13 A. I think, yes, there generally were  
14 minutes that I would have received a copy.

15 Q. Did you retain those?

16 A. I did not in any methodical way retain  
17 records from those meetings.

18 Q. Do you recall ever disposing of minutes  
19 of meetings from the ABT-594 development team?

20 A. I don't recall.

21 Q. Is there a location which you would look  
22 right now for those meeting minutes if you were  
23 trying to track them down?

24 A. My recollection is that these types of

1 pain indication is unlikely to be achieved."

2 Is that consistent with your

3 recollection of what was known about ABT-594 at

4 that time?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. Yes.

8 BY MR. DAVIS:

9 Q. Do you recall discussions within Abbott

10 about the adverse events of nausea, vomiting and

11 dizziness associated with ABT-594?

12 A. There were numerous discussions. I

13 don't know that I can segregate out specific

14 discussions.

15 Q. Do you recall those being areas of

16 concern in the development of ABT-594?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. Can you tell me what you mean by

20 "concern."

21 BY MR. DAVIS:

22 Q. Do you recall people within Abbott

23 expressing the belief that adverse events of

24 nausea, vomiting and dizziness associated with

1 ABT-594 might prevent, for example, its

2 commercialization?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. There were many discussions and much of

6 that hinged around understanding at what doses or

7 plasma concentrations efficacy would be achieved

8 versus at what dose or plasma concentrations

9 adverse events would be -- would be seen.

10 BY MR. DAVIS:

11 Q. As of January 1999 what did you

12 understand to be the dosage at which people who

13 took ABT-594 began to experience adverse events of

14 nausea, vomiting and dizziness?

15 MS. GÜZELSU: Objection.

16 BY THE WITNESS:

17 A. In 1999 -- I can't recall the exact

18 timelines. The first in human trial with ABT-594,

19 nausea and vomiting I believe were first observed

20 at a 150 microgram solution dose. That was my

21 first recollection of nausea and vomiting being

22 recorded as a side effect.

23 BY MR. DAVIS:

24 Q. And it's fair to say that nausea and

1 vomiting encountered in the course of a trial like

2 that, it's not a desirable thing, correct?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. It's certainly not desirable, but it's

6 certainly preferable to many other side effects

7 that one might observe.

8 BY MR. DAVIS:

9 Q. But if you had your druthers in a trial,

10 you would prefer that the drug not exhibit nausea

11 and vomiting in patients. Is that fair to say?

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. Well, actually I'd say that if nausea

15 and vomiting are the dose-limiting side effects,

16 that they're not life-threatening side effects and

17 that they're of less concern than side effects that

18 would indicate effects on cardiac repolarization or

19 liver function or many other types of side effects

20 that are typically seen in drugs.

21 BY MR. DAVIS:

22 Q. If I understand you correctly, what

23 you're saying is if you see nausea and vomiting in

24 the course of a clinical trial of a drug, that's

1 better than seeing something along the lines of  
2 liver toxicity or more serious side effects. Is  
3 that fair to say?

4 A. That's correct.

5 MS. GÜZELSU: Objection.

6 BY MR. DAVIS:

7 Q. But still if you had your choice, you  
8 would prefer not to see nausea and vomiting in the  
9 course of a clinical trial. Is that fair to say?

10 MS. GÜZELSU: Objection.

11 BY THE WITNESS:

12 A. Given that the purpose of a Phase I  
13 trial is to extend dosing until you reach a maximum  
14 tolerated dose, if nausea and vomiting are the  
15 doses -- or are the side effects that define  
16 maximum tolerated dose, that's actually not a bad  
17 thing at all.

18 BY MR. DAVIS:

19 Q. Did it concern you at all in January of  
20 1999 that the analgesic effects of ABT-594 were  
21 associated with adverse events of nausea, vomiting  
22 and dizziness?

23 MS. GÜZELSU: Objection.

24 BY THE WITNESS:

1 A. My recollection is that we were actually  
2 very excited by the results from the Phase I trial  
3 in that a nicotinic NNR compound had never been  
4 demonstrated to show clinical effect in the  
5 treatment of pain in humans. So, that actually was  
6 a very exciting finding.

7 BY MR. DAVIS:

8 Q. Yes, but my -- I guess my question was  
9 somewhat different, was did it concern you at that  
10 point in time that the drug was also associated  
11 with adverse events of nausea, vomiting and  
12 dizziness?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. I don't have any direct recollection of  
16 what my actual level of concern was. In an ideal  
17 world would you like to have a compound that had no  
18 side effects at the dose that showed efficacy in  
19 your very first trial? I think everyone would say  
20 yes.

21 BY MR. DAVIS:

22 Q. At some point in the development of  
23 ABT-594 did you come to believe that the adverse  
24 events of nausea, vomiting and dizziness that were



1 experienced among patients who took ABT-594 could  
2 or likely would limit the commercial success of  
3 that compound if it was introduced by Abbott?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. Could you repeat that, please.

7 BY MR. DAVIS:

8 Q. Sure.

9 MR. DAVIS: Can you reread the question,  
10 please.

11 (WHEREUPON, the record was read  
12 by the reporter as requested as  
13 follows: Q. At some point in the  
14 development of ABT-594 did you come  
15 to believe that the adverse events  
16 of nausea, vomiting and dizziness  
17 that were experienced among  
18 patients who took ABT-594 could or  
19 likely would limit the commercial  
20 success of that compound if it was  
21 introduced by Abbott?)

22 BY THE WITNESS:

23 A. Well, I guess I would have to answer  
24 that that I wasn't in a position to make assessment

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1 of commercial success or lack thereof of any given  
2 compound. That was beyond my responsibilities.

3 BY MR. DAVIS:

4 Q. Do you recall people expressing concerns  
5 in that respect in any of the development team  
6 meetings that you attended?

7 A. I guess I would have to answer that yes,  
8 there certainly was much discussion and it was an  
9 issue, clearly it was an issue related to the  
10 compound.

11 Q. I mean it was an issue that in part was  
12 driving your work in the NNR project to try to come  
13 up with a backup compound or a follow-on compound  
14 and that showed a better tolerability profile, is  
15 that right?

16 MS. GÜZELSU: Objection.

17 BY THE WITNESS:

18 A. Yes.

19 MR. DAVIS: Mark this, please, as the next  
20 exhibit.

21 (WHEREUPON, a certain document was  
22 marked Meyer Deposition Exhibit  
23 No. 2, for identification, as of  
24 01-23-2007.)

1 BY THE WITNESS:

2 A. There are a number of people on this  
3 list that I don't know that I cannot say whether or  
4 not they are -- are Abbott related or --

5 Q. Did you attend this meeting?

6 A. Yes, I did.

7 Q. There is also a reference there to James  
8 Sullivan, Ph.D.?

9 A. Yes.

10 Q. I think you testified earlier today that  
11 you at one point in time reported to Jim Sullivan.

12 Is that the same person?

13 A. Yes.

14 Q. And -- and who is Dr. Sullivan?

15 A. Dr. Sullivan is currently area head vice  
16 president of the neuroscience research group.

17 Q. Does he have any responsibility for the  
18 development of ABT-894 in that capacity, to your  
19 knowledge?

20 A. Yes.

21 Q. What responsibility does he have?

22 A. He serves on a variety of committees  
23 that are responsible for making key decisions on  
24 the development of ABT-894.

1 from 10:08 to 10:16 a.m.)

2 THE VIDEOGRAPHER: And we are back on the

3 video record at 10:16 a.m. This is Tape 2.

4 MR. DAVIS: Let's mark this, please, as the

5 next exhibit.

6 (WHEREUPON, a certain document was

7 marked Meyer Deposition Exhibit

8 No. 3, for identification, as of

9 01-23-2007.)

10 BY MR. DAVIS:

11 Q. Doctor, you have in front of you what's

12 been marked as Exhibit 3 I believe at your

13 deposition.

14 Would you look at the document for a

15 moment and tell me if you have seen it before.

16 A. Yes, I've seen it.

17 Q. This appears to be a transition strategy

18 for ABT-259. Is it fair to say that a transition

19 strategy is sort of the process by which a drug is

20 moved from Discovery into development?

21 A. That's correct.

22 Q. And ABT-259, was that an NNR compound?

23 A. Yes, it was.

24 Q. Was that a compound that you worked on

1 at some point in time during your involvement in  
2 the NNR project?

3 A. Yes.

4 Q. Did you help author this document?

5 A. I believe that I did provide some of the  
6 content for this document, yes.

7 Q. In the page of this document, I think  
8 it's the fourth page of the document, the one that  
9 its Bates number ends in 0597.

10 Do you have that page in front of you?

11 A. Yes.

12 Q. About two-thirds of the way down the  
13 page is a paragraph that begins, "In 1996, ABT-594  
14 was approved for clinical development as a first of  
15 its class ChCM for the treatment of pain."

16 What is ChCM?

17 A. That is synonymous with NNR.

18 Q. And what does it stand for?

19 A. Cholinergic channel modulator.

20 Q. It further states, "Through Phase I and  
21 early Phase II trials, ABT-594 has established  
22 proof of principle for this class, exhibiting  
23 analgesic efficacy in a molar extraction trial."

24 What does it mean that ABT-594 has

1 established proof of principle?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. It means that clinical effectiveness of

5 this compound has been established and that it

6 represents by inference indication that the

7 mechanism is a valid mechanism for treatment of

8 pain.

9 BY MR. DAVIS:

10 Q. It's fair to say that ABT-594 was viewed

11 as having established that NNRs could work as a

12 analgesic?

13 A. That's correct.

14 Q. It goes on to say, "Dose-limiting side

15 effects of nausea, emesis and dizziness were

16 observed and the maximum tolerated dose was

17 equivalent to the minimally effective dose in molar

18 extraction."

19 Do you see that?

20 A. Yes.

21 Q. Now, emesis, that's vomiting, is that

22 right?

23 A. Yes.

24 Q. And what it's saying here, if I read it

1 BY THE WITNESS:

2 A. That's correct.

3 Q. And what -- so we make sure we are  
4 talking the same terms. What do you understand to  
5 be a therapeutic window?

6 A. It's the separation between the dose or  
7 the plasma level associated with a -- a response in  
8 treatment of the target indication versus the dose  
9 or plasma concentration associated with the onset  
10 of side effects.

11 Q. Is it fair to say that -- that's fine.

12 I mean, my understanding of therapeutic  
13 window, and see if it's consistent with yours, is  
14 that it's the -- a large therapeutic window would  
15 be one in which the lower end is -- strike that.

16 Make sure we do this correctly.

17 The therapeutic window is really the  
18 range of dosing within which the drug is both  
19 efficacious and reasonably well tolerated by  
20 patients. Is that fair to say?

21 MS. GÜZELSU: Objection. Could you read --  
22 I'm sorry. Could you read the question back,  
23 please.

24 MR. DAVIS: I can restate it.

1 BY MR. DAVIS:

2 Q. Is it fair to say that the therapeutic  
3 window is the range of dosing within which the drug  
4 is both efficacious and reasonably well tolerated  
5 by the patient?

6 MS. GÜZELSU: Objection.

7 BY THE WITNESS:

8 A. My understanding of therapeutic window  
9 is the difference between an effective dose and a  
10 dose that's -- where you no longer have a  
11 tolerable -- tolerability profile that's  
12 acceptable.

13 BY MR. DAVIS:

14 Q. When you say "the difference," you're  
15 talking about the difference in dosing?

16 A. Right.

17 MR. DAVIS: Let's mark this, please, as the  
18 next exhibit.

19 (WHEREUPON, a certain document was  
20 marked Meyer Deposition Exhibit  
21 No. 4, for identification, as of  
22 01-23-2007.)

23 BY MR. DAVIS:

24 Q. Dr. Meyer, you have what has been marked



1 Q. Did you believe, as of early 2000, that  
2 Abbott was likely to need a backup for ABT-594?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. It was the goal of the -- of the project  
6 that I was heading at that time to identify  
7 backups. Whether we would ultimately need a backup  
8 was uncertain.

9 BY MR. DAVIS:

10 Q. Did you think it was more likely than  
11 not that Abbott was going to need a backup for  
12 ABT-594 as of early 2000?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. Based on industry standards, there's a  
16 very high failure rate of Discovery -- of  
17 development compounds. It certainly was the  
18 logical and prudent thing to do to be developing  
19 backups.

20 BY MR. DAVIS:

21 Q. Based on what you knew specific to  
22 ABT-594 at that time, did you think it was more  
23 likely than not that Abbott was going to need a  
24 backup for ABT-594?

1 MS. GÜZELSU: Objection.

2 BY THE WITNESS:

3 A. I guess I would have thought that there  
4 was a pretty high probability that we would need to  
5 have backup compounds.

6 BY MR. DAVIS:

7 Q. And when you say have a backup compound,  
8 meaning that more likely than not ABT-594 would  
9 not -- at some point in time the development of  
10 that compound would be terminated and Abbott would  
11 then pick up hopefully with another NNR compound  
12 that demonstrated better either efficacy and/or  
13 tolerability. Is that fair to say?

14 MS. GÜZELSU: Objection. Could you -- I'm  
15 sorry. Could you read that. That's a long one.

16 (WHEREUPON, the record was read  
17 by the reporter as requested.)

18 BY THE WITNESS:

19 A. Yes, I would have to say it's fair to  
20 say that that's true for virtually all compounds in  
21 early development, that the likelihood that they  
22 will fail is greater than the likelihood that they  
23 will succeed.

24 Whether I thought 594 was -- had a

1 higher or lower probability of success relative to  
2 other compounds or stand -- or other generic  
3 compounds, let's say, that would be in a  
4 development -- similar state of development, I  
5 really didn't know. I just didn't know.

6 BY MR. DAVIS:

7 Q. Well, are you saying that you -- Abbott  
8 was pursuing a backup and/or follow-on for ABT-594  
9 at this point in time simply because it thought  
10 statistically ABT-594 was not likely to survive the  
11 development process?

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. Well, it's our policy in general that we  
15 strive to identify backup compounds across many,  
16 many programs. And the relative chance for success  
17 or failure is one of many factors that go into a  
18 decision about how much effort you want to put into  
19 a backup program.

20 BY MR. DAVIS:

21 Q. Were there characteristics of ABT-594  
22 that you knew about at this point in time, in early  
23 2000, that led you to believe that it was more  
24 prudent than usual for Abbott to be developing a

1 (WHEREUPON, a certain document was  
2 marked Meyer Deposition Exhibit  
3 No. 5, for identification, as of  
4 01-23-2007.)

5 BY MR. DAVIS:

6 Q. Doctor, you have what's been marked as  
7 Exhibit 5. Let me ask you if you have seen this  
8 document before.

9 A. I don't recognize it.

10 Q. This appears to be a reference to  
11 clinical studies for ABT-594. Did you play any  
12 role in any of the clinical studies involving  
13 ABT-594?

14 A. Could you clarify what you mean by  
15 "role"?

16 Q. Well, did you have any involvement in  
17 those clinical studies in any way?

18 A. I attended meetings where aspects of the  
19 clinical development were discussed. I did not  
20 have any direct involvement in the design or  
21 execution of any of the clinical studies.

22 Q. Did you attend the meetings of the  
23 ABT-594 development team while any of these  
24 clinical studies were underway?

1 A. I frequently attended those meetings.

2 Not every one, but frequently.

3 Q. Do you recall any discussions at any of  
4 the ABT-594 development team meetings in which  
5 preliminary results from any clinical studies of  
6 ABT-594 were discussed?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. Could you clarify what you mean by  
10 "preliminary results"?

11 BY MR. DAVIS:

12 Q. Any data obtained or received from any  
13 clinical trials that were underway.

14 A. During the execution of trials, we would  
15 receive information about enrollment status,  
16 blinded data on dropout rate so we knew from a  
17 given number of subjects that entered the trial,  
18 how many dropped out. We would receive blinded  
19 data on adverse event reporting.

20 Q. Do you recall discussions about any of  
21 the preliminary data that was received while the  
22 trial was underway?

23 A. These topics were discussed at these  
24 meetings.

1 Q. Do you recall any preliminary  
2 conclusions being drawn from any of the preliminary  
3 data received while the trials were underway?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. I'm not exactly sure what you mean by  
7 "preliminary conclusions."

8 BY MR. DAVIS:

9 Q. Do you recall -- there were discussions  
10 about preliminary data at the ABT-594 development  
11 team meetings. Do you recall discussions about  
12 what the data may have meant or foretold for the  
13 compound?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. I don't recall specific discussions  
17 about speculating about what that might mean.  
18 There was -- there were too many unknown pieces at  
19 that point to draw any meaningful conclusions.

20 BY MR. DAVIS:

21 Q. Do you recall anyone drawing any  
22 preliminary conclusions or stating any preliminary  
23 conclusions in the course of any ABT-594  
24 development team meetings while clinical trials

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1 M99-114 trial as the trial was underway was  
2 consistent with the information about the  
3 therapeutic window of ABT-594 that had been  
4 obtained in the Phase I trials?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. There is no therapeutic window in a  
8 Phase I trial. Therapeutic window is indicative of  
9 you are measuring adverse events in the context of  
10 an efficacy readout. Phase I had no efficacy  
11 readout.

12 BY MR. DAVIS:

13 Q. Well, going into the -- can I call it  
14 the 114 study? Do you understand that I'm  
15 referring to the M99-114 study?

16 A. Yes.

17 Q. Going into the 114 study, was it your  
18 understanding that ABT-594 likely had a narrow  
19 therapeutic window?

20 MS. GÜZELSU: Objection.

21 BY THE WITNESS:

22 A. That was a trial in diabetic neuropathy.  
23 We had previous experience in a very small trial in  
24 neuropathic pain indicating that we observed

1 efficacy in a subset of subjects or patients in  
2 that trial subdivided by diabetic neuropathy versus  
3 other neuropathic pain conditions, and so we -- we  
4 knew we had efficacy actually at quite low dose at  
5 that initial trial.

6 We didn't know what to expect in the 114  
7 trial in terms of the level of efficacy we would  
8 observe or at what doses we would observe it.

9 I think we were actually all very  
10 encouraged by the status of the compound at that  
11 point in that we had seen efficacy at a 75  
12 microgram dose in a very small trial with very few  
13 adverse events in that trial.

14 Q. Let me go back to my question, though.

15 Was it your understanding as of the time  
16 that Abbott was entering into the 114 trial that  
17 ABT-594 likely had a very narrow therapeutic  
18 window?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. Actually, no. We didn't have that  
22 understanding because we didn't have an  
23 understanding at all about what the expected  
24 therapeutic index or therapeutic window would be in



1 a chronic pain trial in diabetic neuropathy.

2 BY MR. DAVIS:

3 Q. You mentioned a few moments ago that you  
4 recall discussions among the development team while  
5 clinical trials were underway in which you thought  
6 that the preliminary data that was coming in was  
7 consistent with what you knew about ABT-594 or what  
8 you believed to be true about ABT-594 before the  
9 trial began.

10 Is that a reference to data that was  
11 coming in during the 114 trial?

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. That was reference to that the types of  
15 adverse events that we saw in a blinded fashion, in  
16 the 114 trial, were the same types of adverse  
17 events that we saw in the Phase I trials.

18 BY MR. DAVIS:

19 Q. What, if anything, did that lead you to  
20 believe at that time, without necessarily knowing  
21 for sure?

22 A. It led us to believe that at least one  
23 or more of the doses that were studied in that  
24 trial were producing a significant level of adverse

1 events.

2 Q. Did you regard that as a positive or

3 negative factor or development?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. It was all going to be dependent upon

7 the outcome from the trial. It -- it may -- at

8 that point in time, there was no reason to believe

9 that there were not going to be -- sorry. I have a

10 negative answer or double negative.

11 But there was no reason to believe that

12 there wouldn't be an acceptable dose from that

13 trial.

14 BY MR. DAVIS:

15 Q. Do you recall any discussions among the

16 development team while the 114 trial was underway

17 that -- in which anyone expressed the view that

18 based on the preliminary results from that trial,

19 it appeared less likely that ABT-594 would be

20 further developed by Abbott?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. I do not recall anyone expressing that

24 opinion.

1           However, the meaningful data in terms of  
2           what we were trying to do pre-clinically was  
3           derived from our Phase I data and the earlier  
4           Phase II data where we had quantitative data to --  
5           to correlate dose and plasma exposure to effect.

6           Q.   Is it fair to say that based on what you  
7           saw preliminarily from the 114 trial you still  
8           thought that any backup for ABT-594 was going to  
9           have to demonstrate improvements in emesis, nausea  
10          and dizziness?

11          MS. GÜZELSU: Objection.

12          BY THE WITNESS:

13          A.   Well, since we didn't know how that data  
14          was going to unfold in terms of were there going to  
15          be robust clinical effects at well tolerated doses,  
16          we didn't know.

17          MR. DAVIS: Let's mark this as the next  
18          exhibit, please.

19               (WHEREUPON, a certain document was  
20               marked Meyer Deposition Exhibit  
21               No. 9, for identification, as of  
22               01-23-2007.)

23          BY MR. DAVIS:

24          Q.   Dr. Meyer, you have what's been marked

1 completely beyond my area of expertise or  
2 involvement in the program. This much more was  
3 related to the -- a functional execution of the  
4 program that I really didn't have any direct input  
5 into.

6 BY MR. DAVIS:

7 Q. Do you recall any discussion regarding  
8 what impact ending that 114 study or ending  
9 enrollment for the 11 study -- 114 study -- let me  
10 strike that. Go back.

11 Do you recall any discussion within  
12 Abbott regarding what effect ending enrollment for  
13 the 114 study early might have on the results of  
14 that study?

15 MS. GÜZELSU: Objection.

16 BY THE WITNESS:

17 A. My recollection was that it was felt  
18 that we would be able to get meaningful results and  
19 be able to interpret the trial results based on the  
20 enrollment that had been achieved in the trial at  
21 that point when that decision was made.

22 BY MR. DAVIS:

23 Q. When you say you understood that Abbott  
24 expected it could get meaningful results, does that

1 mean that Abbott understood that all of the goals  
2 of the trial would be -- still able to be  
3 accomplished even if the trial was ended early?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. My recollection is, and this dealt very  
7 heavily with statistical discussions that are  
8 beyond my area of understanding or expertise, but  
9 my recollection is that the feeling was that there  
10 would be sufficient statistical power to make  
11 assessments of the effectiveness across the dose  
12 ranges.

13 BY MR. DAVIS:

14 Q. Do you recall any discussion in the late  
15 2000, early 2001 time frame that all that Abbott  
16 hoped to obtain out of the 114 study, after it  
17 was -- ended early, was proof of efficacy?

18 A. No, I don't recall any discussion like  
19 that.

20 Q. Do you recall any discussion that  
21 Abbott's ability to obtain useful information  
22 regarding anything other than efficacy might be  
23 compromised by ending the trial early?

24 MS. GÜZELSU: Objection.

1 BY THE WITNESS:

2 A. I don't have any recollection of any

3 discussion like that.

4 Q. Was the 114 trial intended to obtain  
5 data for Abbott beyond simply establishing efficacy  
6 of ABT-594?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. I'm the wrong person to ask that. I  
10 didn't design the trial and/or design it in such a  
11 way as to determine what end points could be  
12 measured.

13 BY MR. DAVIS:

14 Q. Do you recall any discussion within  
15 Abbott regarding what effect ending the 114 trial  
16 early would have on Abbott's ability to utilize the  
17 results of that trial to determine the maximum  
18 tolerated dose of ABT-594 for diabetic neuropathy?

19 A. I don't recall any discussion like that.

20 MR. DAVIS: Let's mark this, please, as the  
21 next exhibit.

22 (WHEREUPON, a certain document was  
23 marked Meyer Deposition Exhibit  
24 No. 10, for identification, as of

1 probability that the results of the 114 study were  
2 going to indicate that the safety profile for  
3 ABT-594 was unmet?

4 MS. GÜZELSU: Objection.

5 BY MR. DAVIS:

6 Q. The desired safety profile for ABT-594  
7 was unmet.

8 MS. GÜZELSU: Objection.

9 BY THE WITNESS:

10 A. I was involved in a number of meetings  
11 where probability assessments were made. But I  
12 can't remember the time frame or what data were  
13 available when those were being made.

14 So, I don't have any specific  
15 recollection of probability assessments being made  
16 at this point in time as to whether or not we would  
17 meet the safety criteria.

18 BY MR. DAVIS:

19 Q. Is it fair to say, Dr. Meyer, that in  
20 early 2001, you and other people within Abbott  
21 recognized based on the preliminary data that had  
22 been received on the 114 trial that it was unlikely  
23 that ABT-594 would continue development within  
24 Abbott and that there was a renewed emphasis on

1 developing or focusing on coming up with a backup

2 or follow-on to that compound?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. I do not recall there being a renewed

6 emphasis at that point in time as distinct from

7 there being an emphasis on identification of

8 backups throughout a much longer period of time

9 from the time I joined the program or the time I

10 became project leader going forward. That was

11 always our -- our emphasis.

12 BY MR. DAVIS:

13 Q. Well, is it fair to say that in the,

14 say, January to February time frame of 2001 that

15 you and others within Abbott recognized, based on

16 the preliminary results of the 114 trial, that it

17 was unlikely that Abbott would continue to develop

18 ABT-594 after the results, the final results, of

19 that trial were unblinded?

20 MS. GÜZELSU: Objection.

21 BY THE WITNESS:

22 A. Until the results were unblinded, we

23 didn't know.

24 BY MR. DAVIS:



1 Q. I think my question, however, is a  
2 little bit different.

3 My question is: Is it your  
4 understanding or belief in January or February 2001  
5 that based on the preliminary data that you had  
6 seen from the 114 trial, that it was unlikely that  
7 Abbott would continue to develop ABT-594 after the  
8 final results of that study were unblinded?

9 MS. GÜZELSU: Objection.

10 BY THE WITNESS:

11 A. I don't think that at that point in time  
12 we had seen anything from the trial based on the  
13 unblinded results that fundamentally changed our  
14 understanding of the properties of the compound.

15 So, no, I don't really think that we  
16 were -- had seen anything from the trial that left  
17 us so discouraged as to come to a preliminary  
18 conclusion that the trial was not going to be  
19 successful.

20 BY MR. DAVIS:

21 Q. Do you recall any discussion within  
22 Abbott in the, say, first quarter of 2001 that  
23 Abbott was probably going to terminate development  
24 of ABT-594?

1 MS. GÜZELSU: Objection.

2 BY THE WITNESS:

3 A. No.

4 BY MR. DAVIS:

5 Q. You never heard that?

6 A. I never -- I don't recall anyone saying  
7 to me that they felt that it was likely that it was  
8 going to be terminated.

9 Q. Would you turn to the page that's  
10 numbered 7876, please. There's a slide there  
11 titled "Determining Sample Size and Power."

12 Do you see that?

13 A. Yes.

14 Q. Do you recall any discussion within  
15 Abbott around the determining the sample size and  
16 power of the 114 study in around early 2001?

17 A. I recall that it was a subject of  
18 discussion at various team meetings.

19 Q. Do you recall discussions at team  
20 meetings that the ending enrollment for the 114  
21 study prior to schedule had affected the sample  
22 size and the power of that study?

23 A. I guess my recollection is that the  
24 statisticians who understood all of this, which I

1 do not, felt that we were going to be able to  
2 interpret the results based on a smaller sample  
3 size, and that's what -- the information that we --  
4 that, as I understood it, was coming from the  
5 statistical analysis.

6 Q. I think my question is slightly  
7 different, which is: Do you recall any discussions  
8 within Abbott in the, say, January or February 2001  
9 time frame in which it was discussed -- there was a  
10 discussion concerning the effect that ending the  
11 114 trial early would have on the sample size and  
12 power of that study?

13 MS. GÜZELSU: Objection. Ending the trial  
14 early or ending enrollment early?

15 MR. DAVIS: On -- well, I think the documents  
16 state that they -- the enrollment was ended two  
17 months prior to schedule.

18 MS. GÜZELSU: Enrollment.

19 BY THE WITNESS:

20 A. I don't recall discussion indicating  
21 that there was a feeling that by ending the  
22 enrollment early, that it was going to leave the  
23 trial un -- underpowered and unable to be  
24 interpreted.

1 next exhibit.

2 (WHEREUPON, a certain document was

3 marked Meyer Deposition Exhibit

4 No. 11, for identification, as of

5 01-23-2007.)

6 BY MR. DAVIS:

7 Q. Dr. Meyer, you have what's been marked

8 as Exhibit 11 at your deposition. Will you take a

9 few minutes and look at this document and tell me

10 whether you have seen it before.

11 A. I recognize it, yes.

12 Q. These appear to be slides from a project

13 review for ABT-089 and ABT-594 that was conducted

14 on February 2, 2001.

15 Did you attend that review?

16 A. I believe I did.

17 Q. Dr. Meyer, is this a different review

18 than the review that Dr. Leiden attended that was

19 referred to in Exhibit 10?

20 A. I think it is.

21 Q. Do you recall any discussion within

22 Abbott why it was that Abbott was undertaking yet

23 another review of ABT-594 in early February 2001

24 after having just conducted a project review in

1 January of 2001?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. I don't know. We seem to have lots of  
5 reviews.

6 BY MR. DAVIS:

7 Q. Is it fair to say that they told you to  
8 show up and you would do as you were instructed?

9 A. I think that would be fair to say, yes.

10 Q. And do you recall for whom -- strike  
11 that.

12 Do you recall who attended this  
13 particular project review in early February 2001?

14 A. I do not recall.

15 Q. And do you recall any discussion at that  
16 project review, the February 2, 2001 project  
17 review, regarding any preliminary results from the  
18 114 study?

19 A. I don't recall.

20 Q. Why was it that Abbott was undertaking a  
21 project review of ABT-089 and ABT-594 in the same  
22 meeting?

23 MS. GÜZELSU: Objection.

24 BY THE WITNESS:

1 A. These were both NNR compounds. That's  
2 how they were related.

3 BY MR. DAVIS:

4 Q. Did you regard one compound as having a  
5 greater chance of success at that point in time?

6 A. The compounds were for completely  
7 different indications. At that point in time I  
8 can't even recall exactly where 089 was in the  
9 development cycle. So, I don't recall what  
10 information we had about it.

11 So, I -- I couldn't say whether it was  
12 more or less likely that one or the other had a  
13 greater probability of success.

14 Q. The ABT-089 that's referred to in this  
15 document, Exhibit 11, I take it that's the same  
16 ABT-089 that we were talking about earlier today  
17 that is still under development by Abbott?

18 A. Yes.

19 Q. All right. When did Abbott first begin  
20 development of ABT-089, if you recall?

21 A. Yeah, I don't recall. It's had a -- an  
22 on and off history. It went -- it was originally  
23 put forward as a development candidate a long time  
24 ago. A decision was made not to develop it, and

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1 to your knowledge, that development team  
2 meetings -- that minutes be kept of those meetings  
3 and circulated?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. I don't know what was standard practice  
7 for other development teams. I didn't -- was not a  
8 participant of other development teams.

9 MR. DAVIS: Let's mark this as the next  
10 exhibit, please.

11 (WHEREUPON, a certain document was  
12 marked Meyer Deposition Exhibit  
13 No. 12, for identification, as of  
14 01-23-2007.)

15 BY MR. DAVIS:

16 Q. Dr. Meyer, you have what's been marked  
17 as Exhibit 12 at your deposition and it appears to  
18 be an e-mail from Dr. McCarthy, Dr. Bruce McCarthy,  
19 to Ms. Kowaluk and others at Abbott concerning the  
20 DSG.

21 Do you see that?

22 A. Yes.

23 Q. And the e-mail is dated February 2, '01.

24 Do you recall being asked or

1 participating in a DSG process for ABT-594?

2 A. Yes, I do.

3 Q. And what was -- what was that process?

4 Let me strike that.

5 What was the goal of that process?

6 A. The goal of DSG process was portfolio

7 review to assess the probability of scientific,

8 regulatory, commercial success of various

9 development programs and to evaluate them in the

10 context of all other development programs.

11 Q. How long did this -- was there a certain

12 committee set up or group set up within the DSG for

13 purposes of providing a recommendation on go/no go

14 for ABT-594?

15 MS. GÜZELSU: Objection.

16 BY THE WITNESS:

17 A. I do not believe that it was the

18 specific goal of the DSG team or the DSG process to

19 reach a go/no go on any specific compound.

20 The goal was to evaluate each

21 development compound relative to other development

22 compounds in terms of likelihood of success and

23 commercial value and so forth of one development

24 compound versus another.



1 meetings?

2 A. Yes.

3 Q. This e-mail, again, it's dated

4 February 2, 2001, which I notice the same date as

5 the project review that's referenced in Exhibit 11.

6 Do you see that?

7 A. Yes.

8 Q. The e-mail says, second paragraph, "When

9 we discuss scope and frame during our first

10 meeting, we will want to discuss several issues

11 that came up at today's Leiden meeting (though I

12 think that these are not necessarily new)."

13 Do you recall what discussions came up

14 at that February 2, 2001 meeting with Dr. --

15 project review meeting with Dr. Leiden concerning

16 ABT-594?

17 A. This as I recall it dealt with existing

18 data that had been generated, the status of the

19 program. I don't recall specifics of -- of -- I

20 don't recall exactly what Dr. Leiden concentrated

21 on during those discussions.

22 Q. Well, the first bullet point under that

23 paragraph states, "Given the results of Phase IIb,

24 what is the value of the currently identified

1 backups."

2 Let me stop there.

3 What were the results of Phase IIb that

4 were known to Abbott as of February 2, 2001?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. My understanding and my recollection is

8 that what we knew at that point in time was the --

9 the blinded results on dropout rate, adverse event

10 reporting and anecdotal results from the study.

11 BY MR. DAVIS:

12 Q. Were those preliminary results taken

13 into account by Abbott in formulating its go/no go

14 recommendation for ABT-594?

15 MS. GÜZELSU: Objection.

16 BY THE WITNESS:

17 A. My recollection is that by the time we

18 started this process in earnest, we had moved into

19 the I guess the April time frame when the results

20 became available. And certainly our decision

21 making on ABT-594 or our discussions to generate

22 the probabilities relating to ABT-594 certainly

23 took into account the actual results of the study,

24 the unblinded results that were available later

1 that spring.

2 BY MR. DAVIS:

3 Q. Did they ever take into account the  
4 preliminary results?

5 A. I don't remember the time frame. My  
6 recollection is that we were -- had or were getting  
7 those results just as we were starting this  
8 process.

9 Q. You don't recall the --

10 A. I do not recall the start date of the --  
11 the DSG meetings, what data we had; and I'm  
12 virtually certain that we had the actual data by  
13 the time we were at some point into the process if  
14 we didn't have it at the very beginning. I just  
15 don't remember.

16 MR. DAVIS: Let's mark this, please, as the  
17 next exhibit.

18 (WHEREUPON, a certain document was  
19 marked Meyer Deposition Exhibit  
20 No. 13, for identification, as of  
21 01-23-2007.)

22 BY MR. DAVIS:

23 Q. Dr. Meyer, this is an e-mail from  
24 Dr. Bruce McCarthy to you, among others, dated

1 February 19, 2001.

2 First ask you if you recall receiving

3 this e-mail at or about that time.

4 A. Yeah, I think I do recall this e-mail.

5 Q. The e-mail states in the first

6 paragraph, "Please note the Scientific Strategy for

7 ABT-594/NNR Tolerability Meeting to take place

8 tomorrow. This meeting is a follow-on to the

9 Leiden review in which a recommendation was heard

10 for a comprehensive strategy to address

11 tolerability issues related to NNRs for pain

12 including ABT-594 and follow-ons."

13 Let me stop there.

14 Do you recall any recommendation being

15 made at the February 2, 2001 project review for

16 ABT-594 that Abbott should conduct a

17 comprehensive -- develop a comprehensive strategy

18 to address tolerability issues relating to ABT-594

19 and other NNRs?

20 A. Well, I guess now that I read this, I do

21 have recollection that Dr. Leiden indicated that we

22 needed to more globally address the NNR

23 tolerability profile with a variety of ideas and --

24 and thinking to -- to further understand how we

1 can -- how we can best optimize this platform.

2 Q. And did Dr. Leiden make that

3 recommendation or that request after he had been

4 presented with some of the preliminary data

5 regarding the ongoing 114 trial?

6 MS. GÜZELSU: Objection.

7 BY THE WITNESS:

8 A. I -- I don't recall what data he was

9 using to make that assessment.

10 BY MR. DAVIS:

11 Q. Do you recall in this time frame that

12 Dr. Leiden was concerned about tolerability issues

13 associated with ABT-594 and NNRs generally?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. I think that, yes, he was concerned

17 about the general tolerability of this mechanism.

18 BY MR. DAVIS:

19 Q. If you'd look at the third page of

20 Exhibit 13, there is an ABT -- agenda for an

21 ABT-594 tolerability brainstorm discussion. Do you

22 see that?

23 A. Yes.

24 Q. And there's a reference there to "Brief

1 number of years since 594 went into development  
2 and, prior to that, from its preclinical profile  
3 and our experience with other NNRs relative to  
4 their clinical tolerability profile that we  
5 understood what the -- some of the key issues were  
6 relating to tolerability.

7 So, as a continuing issue, it's one that  
8 hadn't gone away by this point in time.

9 Q. What new data did Abbott have as of  
10 February 2001, to your knowledge, that caused  
11 Abbott to focus on tolerability issues involving  
12 ABT-594 in February of 2001?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. To my knowledge there was nothing  
16 specific about that point in time that would  
17 differentiate it from six months before or a year  
18 before.

19 BY MR. DAVIS:

20 Q. Is it your testimony, Doctor, that this  
21 brainstorm discussion involving tolerability issues  
22 and ABT-594 wasn't prompted in any way by any  
23 preliminary results from the 114 trial?

24 MS. GÜZELSU: Objection.

1 BY THE WITNESS:

2 A. Well, I didn't call it. So, I don't  
3 know exactly what prompted it. It was not my  
4 meeting and I can't tell you what the thinking was  
5 for the individuals who did call the meeting.

6 To my knowledge, there was nothing  
7 specific from the 114 trial that triggered this  
8 event.

9 BY MR. DAVIS:

10 Q. The second point on the agenda  
11 references "Individual perspectives on issues and  
12 questions related improving tolerability."

13 Did you understand as of February 2001  
14 that it was going to be necessary for Abbott to  
15 improve the tolerability of ABT-594 in order to  
16 make that a viable compound in the long term?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. At that point in time we still didn't  
20 know. We had incomplete information. We knew the  
21 Phase I profile. We knew information about dropout  
22 rates, about the adverse events that were seen  
23 throughout the entire clinical development program  
24 of ABT-594.

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1 that was quantitative data and that we had a  
2 specific understanding of dose groups and what  
3 responses we observed and plasma levels associated  
4 with it. And we had the dropout data and we had  
5 the adverse event reporting data from the Phase IIb  
6 trial. That's the data we had.

7 Q. Is it fair to say that the dropout data  
8 and the adverse event data that had been received  
9 preliminarily from the 114 trial caused a  
10 heightened level of concern within Abbott regarding  
11 tolerability issues involving ABT-594?

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. As I believe I have said, I did not  
15 believe that the data that we had seen from the  
16 Phase II trial in a blinded fashion was  
17 significantly different than the data that we had  
18 previously seen in our Phase I trials using the  
19 same formulation, the same dosing regimen.

20 So, there was nothing that I had learned  
21 from the Phase IIb blinded data that in any way  
22 changed my interpretation of what we knew or what  
23 we thought we knew or what we understood about NNR  
24 pharmacology relative to adverse events.



1 I can't testify as to what other people

2 might have thought. That's what I thought.

3 BY MR. DAVIS:

4 Q. Did you observe in, say, January -- the

5 first quarter of 2001 a heightened level of concern

6 among others at Abbott regarding tolerability of

7 ABT-594 as a result of any preliminary data that

8 was received from the 114 trial?

9 MS. GÜZELSU: Objection; asked and answered.

10 BY THE WITNESS:

11 A. I don't recall any individuals making

12 any specific statements that they -- that these

13 data were causing a change in their assessment of

14 ABT-594 relative to our current understanding based

15 on the Phase I data.

16 BY MR. DAVIS:

17 Q. Do you recall anyone generally

18 expressing any concern involving tolerability of

19 ABT-594 in that time frame based on any preliminary

20 data from the phase -- from the 114 study?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. I don't recall anybody expressing that

24 to me.

1 from ongoing P II trial."

2 Do you see that?

3 A. Yes.

4 Q. Is that a reference to the Phase II  
5 trial that was underway at that point in time?

6 MS. GÜZELSU: Objection.

7 BY THE WITNESS:

8 A. It seems reasonable that it is since  
9 that was the only ongoing trial as far as I know at  
10 that point in time.

11 BY MR. DAVIS:

12 Q. And then it says "Probable T." And if  
13 you look in the upper right-hand corner, T equates  
14 to terminate. Do you see that?

15 A. I do.

16 Q. Do you recall why it was that Abbott in  
17 this time frame regarded ABT-594 as a probable  
18 terminate?

19 A. No, I don't.

20 Q. Do you recall hearing in the March 2001  
21 time frame that Abbott's management had designated  
22 ABT-594 as a -- a compound that was probably going  
23 to be terminated?

24 A. No.

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1 Q. Do you recall Dr. McCarthy ever giving  
2 you any feedback regarding, in the course of the  
3 DSG work that you performed, regarding what, if  
4 anything, senior management at Abbott had said in  
5 the course of the portfolio review?

6 A. I don't recall any indication from  
7 Dr. McCarthy that there had been any decision or  
8 pending decision made by senior management  
9 regarding ABT-594.

10 MR. DAVIS: Let's mark this as the next  
11 exhibit, please.

12 (WHEREUPON, a certain document was  
13 marked Meyer Deposition Exhibit  
14 No. 16, for identification, as of  
15 01-23-2007.)

16 BY MR. DAVIS:

17 Q. Dr. Meyer, before I ask you about  
18 Exhibit 16, if someone in the early March 2001 time  
19 frame had told you that Abbott's management thought  
20 that they probably would terminate further  
21 development of ABT-594, that would have been news  
22 to you?

23 MS. GÜZELSU: Objection.

24 BY THE WITNESS:

1 A. Meaning -- meaning what?

2 BY MR. DAVIS:

3 Q. Meaning that that would have -- would

4 that have -- that would have been something that

5 you didn't know previously. Is that right?

6 MS. GÜZELSU: Objection. Sorry. Objection.

7 BY THE WITNESS:

8 A. Yes. If someone told me in March 2001

9 or that time frame that ABT-594 had been

10 terminated, that would have been something that I

11 didn't know at that time.

12 BY MR. DAVIS:

13 Q. And if they had told you in, say, the

14 first half of March 2001 that Abbott's management

15 believed that they were probably going to terminate

16 ABT-594, that would have been information that was

17 new to you at that time, is that right?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. Yes.

21 BY MR. DAVIS:

22 Q. Dr. Meyer, you have in front of you

23 Exhibit 16. Have you seen this document before?

24 A. Yes.

1 Q. And what is it?

2 A. It is an internal project review

3 document of the -- reviewing the neuronal nicotinic

4 receptor program.

5 Q. Did you author this document?

6 A. Yes, I did.

7 Q. For what purpose?

8 A. It was written in reference to

9 March 2001 Discovery project review of the

10 nicotinic program with supporting information for

11 those involved in the review. Provided an update

12 of the current status of the nicotinic program.

13 Q. So, was -- so, was this part of the DSG

14 work that you were performing?

15 A. No.

16 Q. Now, if we take a look at the second

17 page of this document, which I think is actually

18 the beginning of the report -- let me ask you

19 first: To whom was this given?

20 A. This was circulated among management of

21 Discovery and also to some people in the

22 development and commercial organization that had

23 direct responsibility or had direct interaction

24 with the program.

1 Q. To your knowledge, did a copy of this go  
2 to Dr. Leonard?

3 A. Yes, I believe he would have received a  
4 copy of this.

5 Q. How about Dr. Leiden?

6 A. Yes, I think he would have as well.

7 Q. In the second page of this document  
8 under "Project Status Summary," it says, "During  
9 the past year the project has continued to focus on  
10 a mechanism-based approach to the identification of  
11 compounds exhibiting retention of broad-spectrum  
12 analgesic activity associated with ABT-594, but  
13 with an improved therapeutic index relative to the  
14 key adverse events of emesis, nausea and dizziness  
15 that have consistently been observed during the  
16 clinical evaluation of ABT-594."

17 Do you see that?

18 A. Yes.

19 Q. Now, when you refer to the "key adverse  
20 events of emesis, nausea and dizziness that have  
21 been consistently" -- "that have consistently been  
22 observed during the clinical evaluation of  
23 ABT-594," were you referring in part to the  
24 preliminary results from the 114 study?

1 A. Only in the context that those adverse  
2 events were observed during that trial.

3 Q. So, what I said is correct, when you  
4 refer to the clinical -- the adverse events that  
5 have been observed during the clinical evaluation  
6 of ABT-594, you're referring in part to the adverse  
7 events that had been observed at that point in time  
8 in the 114 trial?

9 MS. GÜZELSU: Objection.

10 BY THE WITNESS:

11 A. Yes, that's correct.

12 BY MR. DAVIS:

13 Q. This goes on to say that "ABT-594 is  
14 currently completing a Phase IIb trial in diabetic  
15 neuropathy at doses of up to fourfold above the  
16 doses studied in the previous neuropathic pain  
17 trial with the results of that trial expected by  
18 May 2001."

19 That's the 114 study, correct?

20 A. Yes.

21 Q. It says, "It will be critical to the  
22 continuation of the program to demonstrate enhanced  
23 clinical efficacy at these higher doses."

24 Do you see that?

1 program to progress?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. Could you repeat that.

5 BY MR. DAVIS:

6 Q. Sure. Had you been told by anyone in  
7 Abbott's management before you wrote this report  
8 that it was in fact critical that ABT-594  
9 demonstrate efficacy in its Phase IIb trial in  
10 order for that program to be continued?

11 A. No.

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. I don't think that I had -- these  
15 were -- these were my words. I don't recall being  
16 told that.

17 BY MR. DAVIS:

18 Q. So, this is your perspective on what was  
19 happening, is that right?

20 A. Yes.

21 Q. If you take a look at the third page of  
22 this document, the Bates number 4134, there is a  
23 reference there to a SWOT analysis. Do you see  
24 that?



1 A. Yes.

2 Q. And what does SWOT refer to as you  
3 understand it?

4 A. It's analysis of strengths, weaknesses,  
5 opportunities and threats.

6 Q. And one of the strengths that you note  
7 there is that ABT-594 has established proof of  
8 principle for both nociceptive?

9 A. Nociceptive.

10 Q. And neuropathic pain states. Was that  
11 true as of the time you wrote this report?

12 A. That was based on positive results from  
13 the Phase II molar extraction and the Phase IIa  
14 trial in OA and neuropathic pain. So, yes, as best  
15 I knew that that was true.

16 Q. If you take a look at the two pages  
17 further into the document, pages Bates numbered  
18 4136, under "Development Challenges."

19 It says, "The emerging clinical profile  
20 of ABT-594 has significantly limited the potential  
21 market from the preclinical promise of efficacy in  
22 all pain states to a more limited scope of the  
23 treatment of neuropathic pain."

24 Did I read that correctly?

1 A. Yes.

2 Q. When you referenced the emerging  
3 clinical profile of ABT-594, were you referring in  
4 part to the preliminary results from the 114 trial?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. No, I was not. I was referring to the  
8 properties of the compound that we believe limited  
9 its efficacy in acute pain relating to onset of  
10 action and that really was the extent of  
11 non-neuropathic pain data that we had that we could  
12 call on for the conclusion that I reached in that  
13 sentence.

14 BY MR. DAVIS:

15 Q. The next sentence says, "Slow absorption  
16 and slow onset of analgesic effect plus significant  
17 adverse events of emesis, nausea and dizziness have  
18 precluded ABT-594 from the large and lucrative  
19 acute pain and pain associated with osteoarthritis  
20 markets."

21 Did I read that correctly?

22 A. Yes.

23 Q. The significant adverse events of  
24 emesis, nausea and dizziness, were those observed

1 also in the 114 trial?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. Nausea, emesis and dizziness were

5 observed in the 114 trial.

6 BY MR. DAVIS:

7 Q. And you referred to those as significant

8 adverse events in this report, correct?

9 A. I was not specifically referring to the

10 114 trial.

11 Q. But the -- you regarded those adverse

12 events with respect to 594 as significant at this

13 time. Did you not?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. Yes, I did.

17 BY MR. DAVIS:

18 Q. If you take a look at the next page,

19 please, under "Scientific Logic For Drug

20 Discovery." Do you see the section titled

21 "Background"?

22 In that paragraph it states, "Clinical

23 efficacy in trials of molar extraction,

24 osteoarthritis and neuropathic pain achieved with

1 ABT-594 has validated the NNR approach to the  
2 treatment of pain and Abbott alone is in possession  
3 of this information. ABT-594, however, is an  
4 imperfect drug."

5 Stop.

6 How was ABT-594 as of March 2001 an  
7 imperfect drug?

8 A. We knew that it had limited  
9 applicability in acute pain because of onset. We  
10 knew that -- we knew at what level we saw adverse  
11 events and we knew at what level we had seen  
12 efficacy in OA and neuropathic pain from the  
13 Phase IIa trial and we knew that the level of  
14 efficacy in the Phase IIa trials was -- was only  
15 moderate.

16 Q. It says, goes on to say, "Effects were  
17 only modest at the maximum dose of 75 micrograms  
18 BID." That's essentially twice daily, correct?

19 A. Yes.

20 Q. "And the full potential of this  
21 pharmacology will be more clearly revealed when the  
22 results of the ongoing clinical trial and painful  
23 diabetic neuropathy (at doses of 150, 225 and 330  
24 micrograms BID) become available. Dose-limiting

1 side effects of emesis, nausea and dizziness have  
2 made it difficult to reach what we believe should  
3 be the therapeutically relevant plasma  
4 concentrations of ABT-594 required to achieve  
5 maximal efficacy."

6 Let me stop there and say did you see --  
7 as of March 2001, had you seen anything in the  
8 preliminary results of the 114 trial that made you  
9 believe that it would be less difficult for ABT-594  
10 to reach therapeutically relevant plasma  
11 concentrations in light of adverse events of  
12 emesis, nausea and dizziness?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. Well, as I recall, what -- what I meant  
16 when I wrote this was that based on our preclinical  
17 data set, we didn't think that it would be feasible  
18 to reach plasma concentrations associated with  
19 maximal response in an animal model.

20 So, that limited the upward end of our  
21 ability to unequivocally determine exactly how  
22 efficacious this pharmacology could be in the  
23 treatment of pain.

24 BY MR. DAVIS:

1 Q. My question is a little bit different,  
2 though, Doctor. My question is: As of March 2001,  
3 had you seen anything in the preliminary results of  
4 the 114 trial that caused you to believe that your  
5 statement that "dose-limiting side effects of  
6 emesis, nausea and dizziness have made it difficult  
7 to reach what we believe should be therapeutically  
8 relevant plasma concentrations of ABT-594 required  
9 to meet maximal efficacy" was incorrect?

10 MS. GÜZELSU: Objection. I'm so sorry. Could  
11 you read that back.

12 (WHEREUPON, the record was read  
13 by the reporter as requested.)

14 BY THE WITNESS:

15 A. Well, I hate to be dense, but I guess I  
16 don't even -- I don't quite exactly understand what  
17 you're asking.

18 BY MR. DAVIS:

19 Q. Well, did you believe the statement  
20 contained in your report here that "dose-limiting  
21 side effects of emesis, nausea and dizziness have  
22 made it difficult to reach what we believe should  
23 be therapeutically relevant plasma concentrations  
24 of ABT-594 required to achieve maximal efficacy" to

1 be true as of the time that you wrote this report?

2 A. Based on the data that we had collected  
3 from our Phase I trials that enabled us to define  
4 plasma levels associated with specific adverse  
5 events, we felt that we had a reasonably good  
6 understanding of what a maximum tolerated plasma  
7 level concentration would be and we knew that that  
8 was in a range where we would only expect to see  
9 based on the animal studies less than 100 percent  
10 response.

11 That really doesn't speak at all to what  
12 type of clinically meaningful response we might  
13 expect to see at any of the given doses from the  
14 ongoing trial.

15 Q. Is the statement true, to your  
16 knowledge?

17 A. The statement is true based on our data  
18 from the Phase I trials.

19 Q. Did you -- had you seen anything in the  
20 preliminary results of the 114 trial as of  
21 March 2001 which caused you to believe that it  
22 would not in fact be difficult to reach  
23 therapeutically relevant plasma concentrations of  
24 ABT-594 required to achieve maximal efficacy in

1 patients without experiencing the side effects of  
2 emesis, nausea and dizziness?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. That sentence had a lot of not's and  
6 without's in it. Can you help me out with that.

7 BY MR. DAVIS:

8 Q. I will try it again.

9 What I'm trying to determine, Doctor, is  
10 if you had seen anything in the results of the 114  
11 study that caused you to question or to believe  
12 that anything contained in this statement that  
13 begins "dose-limiting side effects" was untrue or  
14 inaccurate in any way?

15 And I take it from your answers that you  
16 hadn't seen anything from that study that caused  
17 you to believe the statement to be untrue or  
18 inaccurate. Is that correct?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. At that point I don't think we had seen  
22 anything from the study that would contribute to  
23 the conclusion one way or the other.

24 BY MR. DAVIS:



1 Q. The adverse side effects of emesis,  
2 nausea and dizziness that you knew had been  
3 experienced in the 114 trial as of March 2001  
4 didn't impact your belief one way or the other on  
5 whether it was likely that the therapeutic window  
6 for ABT-594 would be, say, enlarged as a result of  
7 that trial?

8 MS. GÜZELSU: Objection.

9 BY THE WITNESS:

10 A. We were examining three different dose  
11 groups. We didn't know what adverse events  
12 associated with -- were associated with which dose  
13 group. We didn't know what level of efficacy was  
14 being observed in any of the dose groups. So we  
15 couldn't draw much of a conclusion at all.

16 It may very well have been that the 150  
17 was very well tolerated. We didn't know it at that  
18 point in time. And was highly efficacious. That  
19 was unknown information.

20 I think we can infer based on the number  
21 of adverse events that at least one of the dose  
22 groups had to be contributing significantly to it.  
23 It's simple math. You know that that has to be the  
24 case. But we didn't know which one or to what

1 extent.

2 Q. Did anyone within Abbott perform any  
3 analysis of the preliminary data on -- of the 114  
4 trial before the results were unblinded in an  
5 attempt to try to determine, you know, which of the  
6 dose levels was likely causing emesis, nausea,  
7 dizziness?

8 MS. GÜZELSU: Objection.

9 BY THE WITNESS:

10 A. Not that I'm aware of.

11 BY MR. DAVIS:

12 Q. Your report further says, "Hence, the  
13 challenge facing the project team is to maintain  
14 the broad-spectrum analgesic efficacy of ABT-594  
15 across models of acute, persistent and neuropathic  
16 pain while decreasing side effect liability,  
17 particularly in models of emesis."

18 Did I read that correctly?

19 A. Yes.

20 Q. The project team you're referring there  
21 is the NNR project team, correct?

22 A. I'm referring to the Discovery team, not  
23 the ABT-594 development team.

24 Q. And, again, the Discovery team is the

1 the actual presentation the document was  
2 presented -- was submitted. But it was a week or  
3 two prior to the meeting. It could have been three  
4 weeks. I just don't remember.

5 Q. If you take a look at the page of  
6 Exhibit 16 that ends in 4142. In the lower  
7 right-hand corner of that page, there is a  
8 reference to "GI Tolerability Profile."

9 Do you see that?

10 A. Yes.

11 Q. And GI is a reference to  
12 gastrointestinal, correct?

13 A. Yes.

14 Q. It says there, "Nausea and emesis have  
15 been identified as significant adverse events  
16 clinically for ABT-594."

17 Do you see that?

18 A. Yes.

19 Q. When you were referencing the  
20 significant adverse events clinically for ABT-594,  
21 were you including the preliminary data from the  
22 114 trial?

23 MS. GÜZELSU: Objection.

24 BY THE WITNESS:

1 A. No, I can definitively say that this did  
2 not because this included specific plasma levels  
3 associated with a specific response. So, these  
4 data were I believe generated by analysis of the  
5 Phase I study using the same formulation as was  
6 used in the Phase IIb diabetic neuropathy trial.  
7 And then although it doesn't show up well in the  
8 graph, it's a plot of plasma level versus percent  
9 emesis comparing the animal model.

10 Q. But you had the preliminary adverse  
11 event data for the 114 trial at the time you were  
12 preparing this document, correct?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. I only had data on the -- from the case  
16 reports that nausea and emesis was observed. I  
17 didn't have any dose or plasma level data to be  
18 associated with that.

19 BY MR. DAVIS:

20 Q. But you had data that identified for you  
21 adverse events that had been experienced in the  
22 course of that trial and the nature of the adverse  
23 events, correct?

24 MS. GÜZELSU: Objection.

1 MR. DAVIS: Let's mark this, please, as the  
2 next exhibit.

3 (WHEREUPON, a certain document was  
4 marked Meyer Deposition Exhibit  
5 No. 17, for identification, as of  
6 01-23-2007.)

7 BY MR. DAVIS:

8 Q. Dr. Meyer, you have what's been marked  
9 as Exhibit 17. Let me ask you first if you have  
10 ever seen this document before.

11 A. I think I have seen it, yes.

12 Q. This references core team meeting  
13 minutes. This is the same core team for the DSG  
14 group that we were discussing earlier today that  
15 met concerning a go/no go recommendation for  
16 ABT-594, is that right?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. I believe it is, yes.

20 BY MR. DAVIS:

21 Q. By the way, in looking at Exhibit 15 for  
22 one moment, which is back in the pile, two back, to  
23 the initial portfolio prioritization document.

24 Have you ever seen that document before

1 today?

2 A. I believe I have not.

3 Q. I'm sorry. Directing your attention

4 back to Exhibit 17.

5 You are listed at one of the attendees

6 at a meeting on March 5, '01. Do you recall

7 attending that meeting?

8 A. Not specifically, no.

9 Q. There are a number of points here that

10 are -- that are identified as "The issues raised

11 are summarized below under three broad subject

12 headings."

13 Do you see that?

14 A. Yes.

15 Q. The first one is, "Can the tolerability

16 of ABT-594 be improved, and a therapeutic index be

17 achieved that is consistent with commercial and

18 regulatory and commercial viability, and how."

19 Do you see that?

20 A. Yes.

21 Q. Now, was it your understanding as of

22 March 5, 2001, that the tolerability of ABT-594 had

23 to be improved in order to achieve a therapeutic

24 index that was consistent with regulatory and

1 commercial viability?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. Well, I think we didn't know.

5 BY MR. DAVIS:

6 Q. Well, if I read the question correctly,

7 Dr. Meyer, it's not whether the tolerability of

8 ABT-594 has to be improved in order to achieve one

9 that's consistent with regulatory and commercial

10 viability. It says, "Can the tolerability of

11 ABT-594 be improved."

12 Did I read that correctly?

13 A. Yes.

14 Q. Is it -- is it your understanding that

15 what this DSG core team was looking at was not the

16 question of whether the tolerability of ABT-594 had

17 to be improved, but whether it could be improved?

18 A. I think that that was the thrust of the

19 discussion of how -- how one might go about

20 manipulating therapeutic index.

21 Q. Is it fair to say, Dr. Meyer, that at

22 the time that this meeting took place, it was the

23 understanding of the core team that the

24 tolerability of ABT-594 had to be improved in order

1 to achieve a therapeutic index that was consistent  
2 with regulatory and commercial viability?

3 MS. GÜZELSU: Objection.

4 BY MR. DAVIS:

5 Q. And the question that was presented was  
6 how are we going to go about doing this?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. Well, those are different issues. It  
10 may be sufficient, but that does not mean that you  
11 wouldn't want to improve it. So, we didn't know  
12 whether it was sufficient, but nonetheless that  
13 didn't mean that we wouldn't seek to improve it.

14 BY MR. DAVIS:

15 Q. Well, do you recall any discussion in  
16 the -- in the context of these core team meetings  
17 regarding whether the existing, okay, tolerability  
18 profile of ABT-594 was sufficient to -- to obtain  
19 regulatory and commercial success or viability?

20 A. Can you -- can you read that back to me,  
21 please.

22 Q. Sure. Do you recall discussions in the  
23 context of the core team meetings regarding whether  
24 the existing tolerability profile of ABT-594 was



1 consistent with the one that would be required in  
2 order to make the product regulatorily and  
3 commercially viable?

4 A. I don't recall that type of discussion.

5 Q. You recall a discussion about the need  
6 to improve the tolerability of ABT-594 in order to  
7 make that product regulatorily and commercially  
8 viable?

9 MS. GÜZELSU: Objection.

10 BY THE WITNESS:

11 A. I don't know how to answer that other  
12 than to tell you that we didn't know at this point  
13 in time whether or not we had a commercially viable  
14 product and we weren't going to know until we had  
15 the data to find out.

16 So, yes, we understood what the  
17 tolerability was in an absolute sense, but we did  
18 not know what the tolerability was relative to  
19 where we would see efficacy with the compound.

20 So, we didn't know whether we had a drug  
21 or didn't have a drug at this point in time and we  
22 weren't going to know until we had the data.

23 Q. But in the meantime you'll agree with me  
24 that Abbott was looking into -- already looking

1 into improving the tolerability of ABT-594,

2 correct?

3 A. We were looking into and discussing ways

4 in which we could adjust the tolerability profile

5 of ABT-594.

6 Q. And it's fair to say that Abbott was

7 doing it at this time, in early March, 2001 because

8 Abbott was concerned that the tolerability profile

9 of ABT-594 was such that it would not be

10 regulatorily and commercially viable?

11 MS. GÜZELSU: Objection.

12 BY THE WITNESS:

13 A. We didn't know and it is certainly

14 reasonable to say that if the compound had an

15 improved tolerability profile, that would improve

16 the overall opportunity for regulatory and

17 commercial viability.

18 BY MR. DAVIS:

19 Q. And it's also fair to say that the

20 reason why you were looking into it in early

21 March 2001 was because there was a concern that the

22 drug wouldn't have the necessary profile, the

23 tolerability profile, in order to be regulatorily

24 and commercially viable?

1 MS. GÜZELSU: Objection.

2 BY MR. DAVIS:

3 Q. That's the reason why you were looking

4 at it at that point in time, right?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. We were looking starting from the day I

8 walked into the program in 1998 and we continued to

9 look through March 2001 and beyond that.

10 BY MR. DAVIS:

11 Q. That's the reason why this DSG core team

12 was looking at that issue in early March 2001

13 because there was a concern within Abbott that the

14 tolerability profile of ABT-594 was not going to be

15 sufficient to make the product regulatorily and

16 commercially viable, correct?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. You would have to ask individuals who

20 organized and set up the DSG process, not me.

21 BY MR. DAVIS:

22 Q. That was your understanding of why that

23 core team was meeting in early March 2001, correct?

24 MS. GÜZELSU: Objection.

1 BY THE WITNESS:

2 A. My understanding of the DSG process was  
3 that we were using it as a tool to evaluate the  
4 value of our assets.

5 BY MR. DAVIS:

6 Q. Nothing else?

7 A. I am unaware of any specific event in  
8 March 2001 that prompted a decision to undergo DSG  
9 analysis of this program.

10 Q. The next bullet point, it says -- the  
11 next point says, "What is the therapeutic index  
12 that is consistent with regulatory and commercial  
13 viability? Does it differ for different pain  
14 states?"

15 Do you see that?

16 A. Yes.

17 Q. The bullet point under that says "AEs."  
18 That's a reference to adverse events, correct?

19 A. Yes.

20 Q. "Observed include nausea, emesis,  
21 dizziness and vivid dreams (at high doses)."

22 Did I read that correctly?

23 A. Yes.

24 Q. Was there a discussion in the DSG core

1 team meetings about the adverse events that had  
2 been observed in the course of the 114 trial?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. All of our information relating to  
6 adverse events as they related to the dose of the  
7 drug administered were derived from the trials in  
8 which we knew which adverse events were associated  
9 with which doses.

10 BY MR. DAVIS:

11 Q. So, is it -- do you mean, then, that in  
12 the course of the DSG meetings that took place in,  
13 say, February and early March of 2001, that there  
14 was no discussion of any adverse events that had  
15 been observed in the 114 trial --

16 MS. GÜZELSU: Objection.

17 BY MR. DAVIS:

18 Q. -- up to that point in time?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. I cannot tell you whether adverse events  
22 were spoken of in aggregate as being associated  
23 with administration of the drug as distinct from  
24 adverse events which we could associate with

1 specific doses of the drug.

2 THE VIDEOGRAPHER: I'm sorry. I don't mean to  
3 interrupt. But we are out of tape.

4 MR. DAVIS: Okay. Let's go off the record for  
5 a moment.

6 THE VIDEOGRAPHER: All right. Going off the  
7 video record at 2:55 -- I'm sorry -- 1:55 p.m.

8 (WHEREUPON, a recess was had  
9 from 1:55 to 2:00 p.m.)

10 THE VIDEOGRAPHER: And we are going back on  
11 the video record at 2:00 p.m. This is Tape 4.

12 BY MR. DAVIS:

13 Q. Dr. Meyer, directing your attention  
14 again to Exhibit 17, the reference to "AEs observed  
15 include nausea, emesis, dizziness and vivid dreams  
16 (at high doses)."

17 Do you see that?

18 A. Yes.

19 Q. In what clinical studies of ABT-594 did  
20 patients report vivid dreams at high doses?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. I believe that was in the 14-day Phase I  
24 trial using hard gelatin capsule that extended

1 doses up to I believe 425 micrograms BID.

2 BY MR. DAVIS:

3 Q. Were any -- were there any reports of

4 adverse events involving vivid dreams in the 114

5 trial?

6 MS. GÜZELSU: Objection.

7 BY THE WITNESS:

8 A. I don't remember.

9 MR. DAVIS: Let's mark this as the next

10 exhibit, please.

11 (WHEREUPON, a certain document was

12 marked Meyer Deposition Exhibit

13 No. 18, for identification, as of

14 01-23-2007.)

15 BY MR. DAVIS:

16 Q. Dr. Meyer, you have what has been marked

17 as Exhibit 18. It's an e-mail from Ms. Kowaluk to

18 you, among others, dated March 8, 2001.

19 Have you seen this e-mail before?

20 A. I believe so. Yes, I believe I have.

21 Q. It says, "Thanks to all who attended

22 last Monday's (3/5/01) meeting of the ABT-594/Pain

23 DSG core team."

24 Do you see that?

1 A. Yes.

2 Q. And I take it that's a reference to the

3 same meeting that we see referenced in the minutes

4 for Exhibit 17, is that right?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. I don't know for certain.

8 BY MR. DAVIS:

9 Q. Well, were there more than one meeting

10 of the ABT-594 pain DSG core team on 3/5/01 to your

11 knowledge?

12 A. Not that I know of.

13 Q. The next paragraph states, "The meeting

14 focused on summarizing key issues of concern for

15 ABT-594."

16 Do you see that?

17 A. Yes.

18 Q. Was the tolerability of ABT-594 a key

19 issue of concern for Abbott as of early March 2001?

20 MS. GÜZELSU: Objection.

21 BY THE WITNESS:

22 A. I would believe that tolerability was an

23 issue that was discussed.

24 BY MR. DAVIS:



1 Q. Was it one of the key issues of concern  
2 that's referenced in Ms. Kowaluk's e-mail dated  
3 3/8/01?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. I believe it was.

7 MR. DAVIS: Mark this as the next exhibit,  
8 please.

9 (WHEREUPON, a certain document was  
10 marked Meyer Deposition Exhibit  
11 No. 19, for identification, as of  
12 01-23-2007.)

13 BY MR. DAVIS:

14 Q. Dr. Meyer, you have what's been marked  
15 as Exhibit 19 at your deposition. Ask you to take  
16 a look at this document for a moment and tell me if  
17 you've seen it before.

18 A. I believe I have.

19 Q. This is a notice of a meeting or a  
20 presentation to be made by Dr. Paul Andrews from  
21 the department of physiology at St. George's  
22 Hospital Medical School in London to various people  
23 at Abbott on March 12, 2001, is that right?

24 A. Yes.

1 Q. Did you actually attend this meeting and  
2 presentation?

3 A. Yes, I did.

4 Q. Did you meet Dr. Andrews?

5 A. Yes.

6 Q. Did this meeting with Dr. Andrews relate  
7 in any way to the work of the ABT-594 pain DSG core  
8 team?

9 A. I don't think there was any direct  
10 relationship one to the other.

11 Q. Did you expect that the information  
12 obtained in the course of this meeting with  
13 Dr. Andrews would be utilized by the ABT-594 pain  
14 DSG core team in doing its work?

15 MS. GÜZELSU: Objection.

16 BY THE WITNESS:

17 A. As I recall, Dr. Andrews was brought in  
18 as an expert in mechanisms of nausea and emesis to  
19 provide information to the team that we hoped would  
20 be helpful in helping us understand nausea and  
21 emesis as it associates to nicotinic.

22 BY MR. DAVIS:

23 Q. Including ABT-594?

24 A. Including ABT-594.

1 Q. Was any information or data provided to  
2 Dr. Andrews before this meeting for him to review  
3 in preparation for the meeting?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. Not that I know of.

7 BY MR. DAVIS:

8 Q. You don't recall participating in any  
9 effort to collect data to provide to Dr. Andrews in  
10 advance of the meeting?

11 MS. GÜZELSU: Objection.

12 BY THE WITNESS:

13 A. Not in advance of the meeting.

14 BY MR. DAVIS:

15 Q. When you met Dr. Andrews at this meeting  
16 had he reviewed, to your knowledge, any information  
17 about ABT-594 before the meeting took place?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. I don't know whether he had. To the  
21 best of my knowledge, we presented at the meeting  
22 data to him regarding ABT-594.

23 BY MR. DAVIS:

24 Q. Had you met Dr. Andrews prior to this

1 meeting back in March of 2001?

2 A. No, I don't think so.

3 Q. Have you met him since?

4 A. No.

5 Q. The second page of Exhibit 19 has a

6 meeting agenda for that March 12th meeting. Do you

7 see that?

8 A. Yes.

9 Q. The meeting occurred at Abbott's

10 offices, correct?

11 A. Yes.

12 Q. Here in the United States, correct?

13 A. Yes.

14 Q. The agenda indicates that it started at

15 8:30 a.m. between 8:30 a.m. and 9:45 a.m. with an

16 ABT-594 review including preclinical data and

17 clinical data. Do you see that?

18 A. Yes.

19 Q. You made a presentation regarding the

20 preclinical data, is that right?

21 A. Yes.

22 Q. And Dr. McCarthy made the presentation

23 regarding the clinical data on 594, is that right?

24 A. Yes.

1 exhibit, please.

2 (WHEREUPON, a certain document was

3 marked Meyer Deposition Exhibit

4 No. 20, for identification, as of

5 01-23-2007.)

6 BY MR. DAVIS:

7 Q. Dr. Meyer, you have what's been marked

8 as Exhibit 20 at your deposition. Ask you to look

9 at this document for a moment and tell me if you

10 have seen it before.

11 A. Yes, I have seen this before.

12 Q. When did you first see this document?

13 A. I can't remember whether I may have seen

14 it a day or two before this 23rd meeting or whether

15 this was the first time I saw it on the 23rd.

16 Q. Do you recall learning at some point in

17 time that the results of the 114 study had been

18 unblinded?

19 A. I -- yes.

20 Q. How did you learn that the results had

21 been unblinded?

22 A. I don't recall. I think my boss

23 probably told me.

24 Q. And how does it work within Abbott? Do

1 that would be the date on which the results would  
2 be unblinded?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. I just don't remember.

6 BY MR. DAVIS:

7 Q. Do you recall reviewing the unblinded  
8 results in this form at or about the time that they  
9 were issued?

10 A. I recall seeing these slides at or about  
11 that time.

12 Q. Did you form any conclusions or  
13 preliminary conclusions at that point in time as to  
14 whether it was likely that Abbott would continue to  
15 develop ABT-594 in light of this data?

16 A. My recollection is that based on my  
17 understanding of clinical trial data that this  
18 represented a very robust and encouraging result,  
19 very robust efficacy result.

20 Q. How about safety?

21 A. Certainly there were adverse events  
22 across all three dose groups.

23 Given that we had made pretty  
24 significant progress in ameliorating adverse events

Meyer, Michael David (Linked) 01/23/2007 9:01:00 AM

1 by formulation and dosing regimen, I think that my  
2 assessment at this point in time was that this  
3 probably did not represent a profile that was  
4 acceptable as is, but there was I felt opportunity  
5 for improvement which could bring us well into a --  
6 a range that would make it a potentially acceptable  
7 profile.

8 Q. In or about April or May of 2001 did  
9 you -- do you recall hearing anyone within Abbott  
10 express a contrary view, a view that these results  
11 made it unlikely that Abbott would continue with  
12 the development of ABT-594?

13 A. I think it would be fair to say that  
14 there were a range of opinions. I don't recall  
15 specifics about who may have had what opinion on  
16 the viability based on these data.

17 MR. DAVIS: Let's mark this, please, as the  
18 next exhibit.

19 (WHEREUPON, a certain document was  
20 marked Meyer Deposition Exhibit  
21 No. 21, for identification, as of  
22 01-23-2007.)

23 BY MR. DAVIS:

24 Q. Dr. Meyer, you have what has been marked

1 Q. Dr. Meyer, you have what's been marked  
2 as Exhibit 22 at your deposition.

3 Have you seen this document before?

4 A. I don't think so.

5 Q. Did you participate in the -- strike  
6 that.

7 The DSG core team for ABT-594, did that  
8 continue its work after the results of the 114  
9 study were unblinded?

10 A. I think so. I just -- without having  
11 access to all of my records, I couldn't  
12 unequivocally say that that was the case. But I  
13 think it did.

14 Q. Did you participate in any presentations  
15 after April of 2001 concerning the future status or  
16 future developmental plans for ABT-594?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. I don't recall.

20 MR. DAVIS: Why don't we mark this, please, as  
21 the next exhibit.

22 (WHEREUPON, a certain document was

23 marked Meyer Deposition Exhibit

24 No. 23, for identification, as of



1 01-23-2007.)

2 BY MR. DAVIS:

3 Q. Dr. Meyer, you have what's been marked  
4 as Exhibit 23 at your deposition. Let me ask you  
5 to take a look at this document and tell me if you  
6 have seen it before.

7 A. Well, I've seen many, if not all, of the  
8 slides included in this. I can't unequivocally say  
9 that I saw it in the context of this GPEC review.

10 Q. What is GPEC?

11 A. We go through a lot of acronyms. I  
12 think it's Global Pharmaceutical Executive  
13 Committee.

14 Q. If you take a look at the third page of  
15 this document. Actually, take a look at the second  
16 page, please. You see there is a reference to  
17 "Development Update" and "DSG Analysis" and "NNR  
18 Follow-Ons."

19 Do you see that?

20 A. Yes.

21 Q. And your name follows the reference to  
22 "NNR Follow-Ons"?

23 A. Yes.

24 Q. Do you recall making a presentation to

1 the GPEC committee regarding NNR follow-ons in or  
2 about August of 2001?

3 A. I made numerous presentations on NNR  
4 follow-ons.

5 Q. They begin to bleed together after a  
6 time?

7 A. They in fact do. I guess I did. I  
8 can't say that I specifically remember it.

9 Q. Would you turn to the next page, which  
10 is the ABT-594 August 2001 GPEC review topics. Do  
11 you see that?

12 A. Yes.

13 Q. And the first bullet point says,  
14 "ABT-594 efficacy in neuropathic pain is  
15 significant."

16 The subpoint says, "ABT-594 has a narrow  
17 therapeutic window and efficacious doses are poorly  
18 tolerated as dosed currently."

19 Correct?

20 A. Yes.

21 Q. You were aware before the ABT-114 study  
22 was completed that or you believed before that  
23 study was completed that ABT-594 had a narrow  
24 therapeutic window, correct?

1 MS. GÜZELSU: Objection.

2 BY THE WITNESS:

3 A. I didn't know what the therapeutic

4 window was prior to the unblinding of the study.

5 BY MR. DAVIS:

6 Q. So, the -- is it only because of the 114

7 study that you came to believe or came to

8 understand as of August 2001 that that ABT-594 had

9 a narrow therapeutic window?

10 A. That was the basis for my understanding

11 and, as best I would understand, other people's

12 understandings that ABT-594 had a narrow

13 therapeutic window in diabetic neuropathy, in pain

14 associated with diabetic neuropathy.

15 Q. Is this limited -- is this reference

16 here limited only to diabetic neuropathic pain?

17 MS. GÜZELSU: Objection.

18 BY THE WITNESS:

19 A. In that the lead bullet is -- refers to

20 neuropathic pain, I would assume that the subbullet

21 also does. That would be my understanding.

22 BY MR. DAVIS:

23 Q. And I take it you had no belief before

24 that 114 study was unblinded that ABT-594 had a

1 narrow therapeutic window?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. In neuropathic pain?

5 BY MR. DAVIS:

6 Q. No, not in neuropathic pain, but with

7 respect to -- strike that.

8 Did you understand that ABT-594 had a  
9 narrow therapeutic window with respect to the molar  
10 extraction study?

11 A. Yes.

12 Q. In addition, there had been an earlier  
13 study in osteo -- for ABT-594 addressing  
14 osteoarthritis pain, correct?

15 A. Yes.

16 Q. Did you understand that ABT-594 had a  
17 narrow therapeutic window in that trial?

18 A. It actually appeared to not have a  
19 narrow therapeutic window and we saw very few side  
20 effects in that trial and did observe efficacy.

21 Q. Did you monitor the osteoarthritis pain  
22 trial of ABT-594 while that trial was underway?

23 MS. GÜZELSU: Objection.

24 BY MR. DAVIS:

1 Q. By "monitor," I mean did you review  
2 preliminary data from that trial?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. I don't recall seeing any preliminary  
6 data from that trial.

7 BY MR. DAVIS:

8 Q. So, as you sit here today you wouldn't  
9 know, for example, how the preliminary data from  
10 that trial compared to the preliminary trial from  
11 the 114 trial?

12 A. No, I don't.

13 Q. You don't know relative number of  
14 adverse events, for example?

15 A. Only in retrospect.

16 Q. What do you know about the relative  
17 number of adverse events between those two trials  
18 in retrospect?

19 A. That in the OA trial there were very few  
20 adverse events.

21 Q. And the existence of the -- the  
22 occurrence of adverse events in the 114 trial was  
23 known while the trial was underway, you just didn't  
24 know what specific doses the adverse events

1 pertained to, is that right?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. That's correct.

5 BY MR. DAVIS:

6 Q. How about premature terminations during  
7 the osteoarthritis trial. How do those compare  
8 relative to the 114 trial?

9 A. I don't remember.

10 MR. DAVIS: Let's mark this as the next  
11 exhibit, please. We're up to 24.

12 (WHEREUPON, a certain document was  
13 marked Meyer Deposition Exhibit  
14 No. 24, for identification, as of  
15 01-23-2007.)

16 BY MR. DAVIS:

17 Q. Dr. Meyer, you have what's been marked  
18 as Exhibit 24. Let me ask you to take a look at  
19 this document and tell me if you have seen it  
20 before, please.

21 A. While I recognize the slides starting on  
22 the "Background" section, but the initial slides I  
23 don't recognize.

24 Q. I'm sorry. You recognize the slides

1 Q. Was the decision by Abbott's management  
2 to discontinue development of ABT-594 consistent  
3 with the recommendations that had been made by the  
4 DSG core team?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. I don't think I can answer that because  
8 my part of that only dealt with the evaluation of  
9 one compound, and the overall process put that in  
10 the context of every other development program  
11 within Discovery -- or within the development  
12 portfolio.

13 BY MR. DAVIS:

14 Q. Do you recall where it was that ABT-594  
15 stood relative to the other compounds that were  
16 ranked?

17 A. I --

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. I don't know.

21 MR. DAVIS: Let's mark this, please, as the  
22 next exhibit.

23 (WHEREUPON, a certain document was

24 marked Meyer Deposition Exhibit

Meyer, Michael David (Linked) 01/23/2007 9:01:00 AM

1 No. 26, for identification, as of

2 01-23-2007.)

3 BY MR. DAVIS:

4 Q. Dr. Meyer, I'll show you what's been

5 marked as Exhibit 26 at your deposition and ask you

6 to look at this document for a moment and tell me

7 if you have seen it before, please.

8 A. Yes, I have.

9 Q. The first page appears to be an e-mail

10 that you sent to Dr. Silber and others at Abbott in

11 June of 2002. Is that right?

12 A. Yes.

13 Q. Did you in fact send this e-mail?

14 A. Yes, I believe I did.

15 Q. And these are e-mails -- attached to the

16 e-mail were some slides that you intended to use in

17 making a presentation to the Discovery Decision

18 Committee at that time?

19 A. I think it was Discovery Development

20 Committee.

21 Q. Sorry. I can't keep all the D's

22 straight?

23 A. Nor can I.

24 Q. But attached are slides that you were



1 planning to show to some Abbott committee at that

2 time, right?

3 A. That's correct, yes.

4 Q. If I could just direct your attention to

5 the page of the slides with the Bates number that

6 ends in 8748. Did you prepare this slide?

7 A. Yes, I did.

8 Q. And this slide is titled "ABT-594 Was

9 Discontinued From Clinical Development Based on an

10 Unfavorable Side Effect Profile."

11 Did I read that correctly?

12 A. Yes.

13 Q. Was that statement true at the time that

14 you created the slide?

15 A. Well, I guess I'd have to characterize

16 it as an oversimplification, but it's generally

17 true in that that was a contributing factor to the

18 decision to discontinue.

19 Q. The next bullet point on the slide says,

20 "Key adverse events associated with ABT-594 were

21 nausea, emesis and dizziness."

22 Do you see that?

23 A. Yes.

24 Q. And was that statement true at the time

1 that you prepared the slide?

2 A. Yes.

3 Q. So, the key adverse events that resulted  
4 in the discontinuation of the clinical development  
5 of ABT-594 were nausea, emesis and dizziness, is  
6 that right?

7 A. Those were the dose-limiting adverse  
8 events, yes.

9 Q. That resulted in the discontinuation of  
10 ABT-594 from clinical development, is that right?

11 A. Those adverse events in the context of  
12 doses required to produce efficacy, yes. So, it's  
13 more complicated than simply the adverse events.

14 MR. DAVIS: Actually, why don't we take five  
15 more minutes. I just want to run through the rest  
16 of these and see if I need to -- how much of these  
17 I need to run through. The good news is we are  
18 getting to the bottom of the pile.

19 THE VIDEOGRAPHER: Do you want me to go off  
20 the record?

21 MR. DAVIS: Off the record.

22 THE VIDEOGRAPHER: We are going off the video  
23 record at 2:38 p.m.

24 (WHEREUPON, a recess was had

1 from 2:38 to 2:41 p.m.)

2 THE VIDEOGRAPHER: And we are going back on

3 the video record at 2:41 p.m.

4 MR. DAVIS: Let's mark this, please, as the

5 next exhibit.

6 (WHEREUPON, a certain document was

7 marked Meyer Deposition Exhibit

8 No. 27, for identification, as of

9 01-23-2007.)

10 BY MR. DAVIS:

11 Q. Dr. Meyer, I'll show you what's been

12 marked as Exhibit 27 at your deposition and ask you

13 to look at this document for a moment and tell me

14 if you have seen it before.

15 A. Yes, I have.

16 Q. Did you author or participate in the

17 creation of this document?

18 A. Yes.

19 Q. And this is a presentation or a report

20 regarding a potential development candidate, which

21 is A429202, is that right?

22 A. That's correct.

23 Q. Was this particular compound actually

24 put into development by Abbott?

1 A. Yes.

2 Q. Is it still in development?

3 A. No.

4 Q. When was it terminated?

5 A. I believe it was about midyear 2003.

6 Q. Why?

7 MS. GÜZELSU: Objection.

8 BY MR. DAVIS:

9 Q. If you recall.

10 A. Oh, I do. It produced atrial  
11 fibrillation in one subject.

12 Q. That's some sort of undesirable heart  
13 activity?

14 A. Yes.

15 Q. Was that during Phase I trial?

16 A. That was a Phase I trial, yes.

17 Q. Now, if you look at the page of this  
18 report that is Bates numbered 4001 in the lower  
19 right-hand corner. There is a section titled  
20 "Abbott Approaches and Advances - Clinical  
21 Experience with ABT-594."

22 Do you see that?

23 A. Yes.

24 Q. Based on what you know, Dr. Meyer, is it

1 fair to say that Abbott regards the work that it  
2 did with ABT-594 to have been useful in the sense  
3 that it established the efficacy of or potential  
4 efficacy of NNR compounds?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. Yes.

8 BY MR. DAVIS:

9 Q. If you look at the -- two more pages  
10 into the document, the page that's Bates numbered  
11 4003. There is a reference there to the 114 study  
12 and the results of the 114 study. Do you see that?

13 A. Yes.

14 Q. And there are some charts and then some  
15 additional text all concerning the 114 study. Is  
16 that right?

17 A. That's correct.

18 Q. The -- about halfway down the page there  
19 is a paragraph that states, "The levels of adverse  
20 events were, however, substantial and  
21 dose-related."

22 Do you see that?

23 A. Yes.

24 Q. That's a reference to the 114 study,

1 correct?

2 A. Yes.

3 Q. So, it's correct that the levels of

4 adverse events that were experienced in the 114

5 study were substantial, is that right?

6 A. Yes.

7 Q. And ultimately turned out to be

8 dose-related, correct?

9 A. That's correct.

10 Q. It says, "Adverse event-related

11 discontinuation rates of 28, 46 and 66 percent were

12 realized for the 150, 225 and 300 microgram groups

13 respectively."

14 A. Yes.

15 Q. "Adverse events recorded at levels above

16 placebo are reported in Table 8."

17 It says, "The high dropout rate was

18 driven almost exclusively by adverse events and not

19 a lack of efficacy."

20 Is that all correct?

21 A. Yes.

22 Q. It goes on to say, "In the 300 microgram

23 dose group, adverse events were responsible for

24 66 percent of dropouts versus 9 percent for the

1 placebo group."

2 Is that right?

3 A. Yes.

4 MS. GÜZELSU: Objection.

5 BY MR. DAVIS:

6 Q. So, when you unblinded the results from

7 114, you found that of all the adverse events only

8 9 percent were attributable to placebo, is that

9 right?

10 A. I believe that's correct.

11 Q. And so now 91 percent of the adverse

12 events were attributable to some dosage of ABT-594,

13 correct?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. I can't -- I can't say for certain that

17 that's a correct analysis of the data. Certainly

18 appears that nausea -- placebo accounted for

19 11 percent of nausea, for instance.

20 It may be that taken in aggregate of all

21 adverse events, 9 percent were attributable to the

22 placebo group. But offhand I can't guarantee that

23 that is true.

24 BY MR. DAVIS:

1 Q. That's what you put down here, right?

2 A. I --

3 Q. And you --

4 A. Yes.

5 Q. You obviously understood that to be  
6 accurate at the time that you wrote it here?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. That's correct.

10 MR. DAVIS: Let's mark this, please, as the  
11 next exhibit.

12 (WHEREUPON, a certain document was  
13 marked Meyer Deposition Exhibit  
14 No. 28, for identification, as of  
15 01-23-2007.)

16 BY MR. DAVIS:

17 Q. Dr. Meyer, you have what's been marked  
18 as Exhibit 28 at your deposition. Look at this  
19 document for a moment, please, and tell me if you  
20 have seen it before.

21 A. Yes, I have.

22 Q. What is ABT 5 -- I'm sorry -- what is  
23 ABT-259?

24 A. It was a compound from the nicotinic



1 program that went into development following

2 ABT-594.

3 Q. And is it still being developed by

4 Abbott?

5 A. No.

6 Q. When was it discontinued?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. I think somewhere around 2000. I just

10 don't remember exactly.

11 Q. Why was it discontinued?

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. One of the principal contributing

15 factors was the pharmacokinetic profile with

16 respect to half-life was quite short, and we did

17 not believe that it possessed a profile that would

18 render it a viable candidate for further

19 development.

20 BY MR. DAVIS:

21 Q. Meaning that the -- the efficacious

22 effect, if any, didn't last particularly long in

23 the subjects or was not expected to last long in

24 the subjects?

1 A. Yes.

2 MR. DAVIS: Mark this, please, as the next

3 exhibit. We're up to 29.

4 (WHEREUPON, a certain document was

5 marked Meyer Deposition Exhibit

6 No. 29, for identification, as of

7 01-23-2007.)

8 BY MR. DAVIS:

9 Q. Dr. Meyer, I'll show you what's been

10 marked as Exhibit 29 at your deposition and ask you

11 to look at this document for a moment and tell me

12 if you've seen it before.

13 A. Yes, I have seen this before.

14 Q. Is this a presentation that Dr. Sullivan

15 made at some point in time regarding neuroscience

16 and pain?

17 A. Yes.

18 Q. Do you know to what group this

19 presentation was made or groups?

20 A. I believe it was made to outside

21 investment community.

22 Q. Do you know approximately when it was

23 that Dr. Sullivan first made this presentation?

24 A. As I recall, it was two to maybe three

1 years ago.

2 Q. So, it was sometime in 2004, 2005,

3 roughly?

4 A. I believe so, yes.

5 Q. Were you present when -- at any point in

6 time when Dr. Sullivan made this presentation?

7 A. No.

8 Q. Did you help him prepare this

9 presentation?

10 A. I provided some input.

11 Q. Did you review the presentation before

12 it was made by Dr. Sullivan?

13 A. I think that he provided me with a copy

14 of it prior to when he presented this.

15 Q. Did you look at it when he gave it to

16 you?

17 A. Yes.

18 Q. Did you see anything in it that you

19 thought was inaccurate?

20 A. No.

21 Q. If you take a look at the third page of

22 Exhibit 29, there are a couple of slides there,

23 which make reference under Phase I, do you see

24 there is a reference to ABT-894?

1 A. Yes.

2 MS. GÜZELSU: Objection.

3 BY MR. DAVIS:

4 Q. Has Abbott discussed publicly its  
5 development of ABT-594?

6 A. I'm sorry?

7 MS. GÜZELSU: Objection.

8 BY MR. DAVIS:

9 Q. Has Abbott discussed publicly its  
10 development of ABT-594?

11 MS. GÜZELSU: Objection.

12 BY THE WITNESS:

13 A. To the best of my knowledge, yes, it was  
14 public knowledge.

15 BY MR. DAVIS:

16 Q. And if you'd turn, please, to the  
17 page -- and the pages aren't Bates numbered. But  
18 if you turn to the page that has two slides. One  
19 titled "Neuropathic Pain" and the second titled  
20 "ABT-594 First Generation NNR."

21 A. Yes.

22 Q. You have that page, correct?

23 It says -- do you see the bottom slide  
24 makes reference to ABT-594, right?

1 A. Yes.

2 Q. What is a first generation NNR?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. I believe our reference there would be

6 that it was the first of this class of compounds

7 that we put into development.

8 BY MR. DAVIS:

9 Q. And it says, "Efficacy in multiple

10 clinical models. Efficacy comparable to market

11 leader in neuropathic pain. Limited tolerability.

12 Key issue: Nausea and GI side effects."

13 Are those statements all accurate?

14 A. Yes, I believe so.

15 Q. And if you look at the next page, there

16 is a reference to ABT-894 as the next generation

17 compound. What does it mean to be a next

18 generation compound?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. I think in the context of this

22 presentation it meant that ABT-894 was now our

23 active development compound that we believe met

24 many of the criteria for a -- an improved -- a

1 compound with an improved profile relative to

2 ABT-594.

3 Q. If you look at the next page, there is

4 another slide on "ABT-894: Next Generation NNR."

5 Do you see that?

6 A. Yes.

7 Q. And it says, "Full efficacy without GI

8 side effects."

9 Do you see that?

10 A. Yes.

11 Q. And there are a couple slides there

12 which show efficacy versus side effects. Do you

13 see that?

14 A. Yes.

15 Q. Is it in fact correct that based on

16 Abbott's experience to date ABT-894 demonstrates

17 full efficacy without at least the same level of GI

18 side effects as ABT-594?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. These data are all preclinical data and

22 they are accurate as shown. We have no information

23 about the clinical effectiveness of ABT-894.

24 BY MR. DAVIS:

1 Q. How about the -- any results from the  
2 clinical trials that have been conducted to date  
3 regarding the side effects, GI side effects?

4 A. We do have information.

5 Q. And is that consistent with what we see  
6 in Exhibit 29, that it has a more desirable GI side  
7 effect profile?

8 A. Well, we believe it does. But, of  
9 course, lacking the clinical efficacy data, we  
10 don't know whether it will in fact correspond to an  
11 improved therapeutic index relative to ABT-594.

12 Q. Is there a Phase II trial planned for  
13 ABT-894?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. To the best of my knowledge, yes.

17 BY MR. DAVIS:

18 Q. Do you know when that trial is scheduled  
19 to commence?

20 A. I believe -- I think it's to start later  
21 this year. I don't know the exact schedule of when  
22 we'd anticipate to start that trial.

23 Q. Is that trial for an indication in pain?

24 MS. GÜZELSU: Objection.

1 BY THE WITNESS:

2 A. We're evaluating it in multiple

3 indications, pain being one of them.

4 BY MR. DAVIS:

5 Q. Will the Phase II trial be for a pain

6 indication?

7 A. Pardon?

8 Q. Will the Phase II trial that you

9 understand will be starting later this year, will

10 that be for a pain indication, at least among

11 others?

12 A. That's my understanding, yes.

13 Q. Have you ever had any involvement in any

14 efforts by Abbott to outlicense ABT-594?

15 A. No, I have not been involved in any of

16 that.

17 Q. Have you ever -- are you aware of any

18 efforts by Abbott to outlicense ABT-594?

19 A. I'm not aware of what Abbott might be

20 doing.

21 Q. Ever spoken with Mr. Phil Deemer about

22 ABT-594?

23 A. No.

24 MR. DAVIS: I have no further questions at



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VIA FACSIMILE AND U.S. MAIL

Richard C. Abati, Esq.  
Choate Hall & Stewart LLP  
Two International Place  
Boston, MA 02110

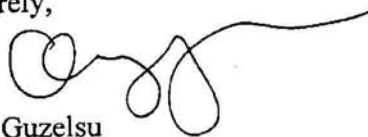
Re: John Hancock Life Ins. Co., et al. v. Abbott Laboratories

Dear Rich:

Dr. Michael Meyer signed the original transcript of his January 23, 2007 deposition. The only correction made is on page 40, line 11: "early 2002" changed to "mid 2001." A copy of the changed page and the signature page is included with this letter.

Please do not hesitate to call if you have any questions or comments.

Sincerely,



Ozge Guzelsu

cc: Jeffrey I. Weinberger, Esq. (w/encl.)  
Gregory D. Phillips, Esq. (w/encl.)  
Eric J. Lorenzini, Esq. (w/encl.)  
Brian A. Davis, Esq. (w/encl.)  
Joseph H. Zwicker, Esq. (w/encl.)  
Andie Cardinale (w/encl.)

MUNGER, TOLLES & OLSON LLP

Richard C. Abati

January 12, 2007

Page 2

bcc: Peter Witty (w/encl.)

1 Q. Again, as you sit here today you don't  
2 recall when it was that ABT-894 was first  
3 discovered?

4 MS. GÜZELSU: Objection.

5 BY THE WITNESS:

6 A. I don't recall the -- the date.

7 BY MR. DAVIS:

8 Q. Was it in the 2001 time frame?

9 A. I think based -- the A numbers are  
10 sequential. Based on that I'm -- I'm guessing  
11 <sup>mid 2001</sup> probably ~~early 2002~~ would be my best estimate.

12 Q. While you were working on the NNR  
13 program, approximately how many molecules were sort  
14 of under consideration or being examined at that --  
15 at any particular point in time?

16 MS. GÜZELSU: Objection.

17 BY THE WITNESS:

18 A. Somewhere in the range of 1,500 to  
19 2,000, perhaps more. But in that general range.

20 BY MR. DAVIS:

21 Q. You mentioned ABT-089. That compound  
22 currently is under development?

23 A. Yes.

24 Q. What's the status of development of that

Page 226

1 UNITED STATES DISTRICT COURT  
2 FOR THE DISTRICT OF MASSACHUSETTS  
3 JOHN HANCOCK LIFE INSURANCE )  
4 COMPANY, JOHN HANCOCK VARIABLE )  
5 LIFE INSURANCE COMPANY and )  
6 MANULIFE INSURANCE COMPANY )  
7 (f/k/a INVESTORS PARTNER )  
8 INSURANCE COMPANY), )  
9 Plaintiffs, ) Civil Action No.  
10 -vs- ) 05-11150-DPW  
11 ABBOTT LABORATORIES, )  
12 Defendant. )  
13

14 I hereby certify that I have read the  
15 foregoing transcript of my deposition given at the  
16 time and place aforesaid, consisting of Pages 1 to  
17 225, inclusive, and I do again subscribe and make  
18 oath that the same is a true, correct and complete  
19 transcript of my deposition so given as aforesaid,  
20 and includes changes, if any, so made by me.

18   
19 MICHAEL DAVID MEYER

20 SUBSCRIBED AND SWORN TO  
21 before me this day  
22 of , A.D. 200\_\_.

23 Notary Public  
24

-- JET45E5992900C1 -----  
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3:39 PM 2/28/2007 Transmission Record

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Used channel 9.

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No AOC data.

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Pages sent: 1 - 4

# **Meyer Deposition Exhibit 1**

**P's Exhibit HV**



Tim  
Vanbiesen /LAKE/PPRD/  
ABBOTT  
03/16/2000 09:18 AM  
To Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT  
cc  
bcc  
Subject Abt. 773 Dosing Strategy Kick-off Meeting

Forwarded by Tim Vanbiesen/LAKE/PPRD/ABBOTT on 03/16/2000 09:18 AM

Keith F Hendricks  
01/26/2000 04:55 PM

To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT,  
Carl Craft/LAKE/PPRD/ABBOTT@ABBOTT, Jerald J Wenker/LAKE/PPD/ABBOTT@ABBOTT,  
Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT, Richard G  
Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Susan J Semla/LAKE/PPRD/ABBOTT@ABBOTT, Robert  
K Flamm/LAKE/PPRD/ABBOTT@ABBOTT, Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Linda E  
Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Charles Locke/LAKE/PPRD/ABBOTT@ABBOTT, Gregory  
Bosco/LAKE/PPRD/ABBOTT@ABBOTT, George Aynilian/LAKE/PPRD/ABBOTT@ABBOTT, Laura  
Robinson/LAKE/AI/ABBOTT@ABBOTT, Jean-Paul Kress/LAKE/AI/ABBOTT@ABBOTT, Nigel  
Livesey/LAKE/AI/ABBOTT@ABBOTT, Jessie R Groothuis/LAKE/AI/ABBOTT@ABBOTT, Bonnie J  
Shaul/LAKE/AI/ABBOTT@ABBOTT  
cc: Steve C Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, Steve Cohen/LAKE/PPRD/ABBOTT@ABBOTT,  
Tim Vanbiesen/LAKE/PPRD/ABBOTT@ABBOTT, mchang@sdg.com, Tony C  
Deahl/LAKE/AI/ABBOTT@ABBOTT  
Subject: Abt. 773 Dosing Strategy Kick-off Meeting

Greetings,

We now need to turn our attention to the very important task of formulating the dosing strategy for Abt 773. Mark Chang, of SDG, will be facilitating the decision-making process along with 2-3 other Abbott personnel. The likely core team for this assessment is shown below, but this can be discussed and finalized at the kick-off meeting. The kick-off meeting will be from 1-5 on Monday, January 31st. The location has not yet been determined.

As we discussed in our last meeting, the timeline for completing this assessment will be tight, so it will most certainly require calendar prioritization from all of us. But as we also discussed, there is no more important issue for us to make a decision on right now in our entire portfolio, so the time will be well spent. However, Mark will try to organize the activities to make the most efficient use of our valuable time as possible.

Given the time constraints, it is especially important for as many of you as possible to be at the kick-off meeting. I look forward to seeing you there.

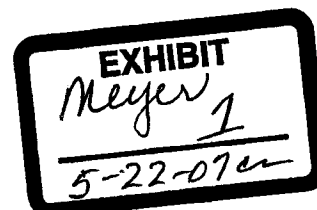
Regards,

Keith Hendricks

PPD Team Members :

David D Morris  
Carl Craft  
Rosemarie K Waleska  
Richard G Granneman  
Susan J Semla

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ABBT305783

Robert K Flamm  
Rod M Mittag  
Linda E Gustavson  
Charles Locke  
Greg Bosco  
George Aynlian

AI Team Members :  
Keith Hendricks  
Nigel Livesey  
Laura Robinson  
Jean-Paul Kress  
Jessie Groothuis  
Bonnie Shaul

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ABBT305784



## **Meyer Deposition Exhibit 3**

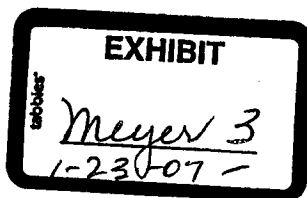
**P's Exhibit HW**

# ABT-259

## Transition Strategy



April 1999



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ABBT 0020594

**ABT-259 Transition Strategy**

- I. INTRODUCTION AND BACKGROUND (Mike Meyer)**
- II. TRANSITION STRATEGY (Olga Jasinsky)**
- III. TRANSITION PROGRAM**
  - 1. Drug Substance Synthesis (deliveries) (Steve King)**
    - a. D-45L**
    - b. CAPD**
    - c. Analytical Method (Jim Morley)**
  - 2. Formulation Development (Howard Cheskin/Lloyd Dias/Jim Morley)**
    - a. Liquid Formulation**
    - c. Analytical**
    - b. Solid Formulation**
  - 3. Toxicology (Bill Bracken/Julia Hui)**
    - a. Genotoxicity Studies (Ron Snyder)**
    - b. Acute Studies**
  - 4. Drug Analysis (Peter Bryan/Tawakol El Shourbagy)**
    - a. Method Development**
    - b.**
  - 5. Pharmacokinetics (Walid Awni/Ritu Lal)**
    - a. Preclinical**
    - b. Clinical Objectives**
  - 6. Metabolism (Joe Machinist/ Stan Roberts)**
    - a. Protein Binding**
    - b. Metabolism/Excretion Rats**
    - c. In vitro-Metabolism**
    - d. P-450**
  - 7. Clinical (Olga Jasinsky)**
    - a. Single Rising Dose First Time in Man (Phase I)**
    - b. Single Dose Molar Extraction (Phase II)**

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**ABBT 0020595**

**IV. FUTURE DEVELOPMENT**

- 1. Drug Substance Deliveries (Steve King/ Dave Riley/Jim Ciullo)**
- 2. Formulation Development (Lloyd Dias/ Howard Cheskin)**
- 3. Toxicology (Julia Hui/Bill Bracken)**
- 4. Drug Analysis (Peter Bryan/ Tawakol El Shourbagy)**
- 5. Pharmacokinetics (Ritu Lal/ Walid Awni)**
- 6. Metabolism (Joe Machinist/Stam Roberts)**
- 7. Clinical (Olga Jasinsky)**

**V. RISK ASSESSMENT/KEY ISSUES (All)**

**VI. TIMELINES MILESTONES (All-Olga Jasinsky)**

- 1. Transition Program**
- 2. Future Development**

**VII. DEVELOPMENT COSTS (All-Olga Jasinsky)**

- 1. Transition Program**
- 2. Future Development**

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**ABBT 0020596**

## I. INTRODUCTION AND BACKGROUND

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. US costs are estimated at \$100 billion a year in direct and indirect costs. Approximately 95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain. However, there have been few major advances in pain therapy over several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics. Recent findings in the understanding of pain mechanisms have led to a new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development.

One new approach being explored for the development of novel analgesics is through modulation of nicotinic acetylcholine receptors (nAChRs). The concept that cholinergic channel modulation (ChCM) may be involved in modulating pain pathways is not new. Nicotine has been known for over 60 years to have antinociceptive actions. More recent studies have shown that microinjection of (-)-nicotine into some of the same CNS sites where morphine is active can elicit potent antinociception. However, peripherally administered (-)-nicotine is a very poor analgesic agent because of its extremely short duration of action (less than 10 minutes) and because its effects occur at doses only 4-fold lower than the approximate lethal dose. In contrast, epibatidine, a naturally occurring alkaloid recently isolated from the Ecuadorian frog *Epipedobates tricolor*, produces antinociceptive effects via interactions with nAChRs, and is 200-fold more potent than morphine.

In 1996, ABT-594 was approved for clinical development as a first of its class ChCM for the treatment of pain. Through Phase I and early Phase II trials, ABT-594 has established proof-of-principle for this class, exhibiting analgesic efficacy in a molar extraction trial. Dose-limiting side effects of nausea, emesis and dizziness were observed, and the maximum tolerated dose was equivalent to the minimally effective dose in molar extraction. Phase II trials in neuropathic pain and osteoarthritis are continuing.

ABT-259 is a non-opioid, non-NSAID analgesic follow on to ABT-594, that is differentiated from the latter based on an improved side effect profile in animal models of emesis, cardiovascular and CNS side effects, and acute toxicity. ABT-259 exhibits comparable potency and efficacy to ABT-594 across animal models of acute, persistent and neuropathic pain. Like ABT-594, ABT-259 retains efficacy on repeated dosing. Moreover, ABT-259 has a nearly identical pharmacokinetic and metabolic

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ABBT 0020597

profile to ABT-594. ABT-259 does not exhibit a morphine-like profile in models of physical addiction and drug-seeking behavior.

ABT-259 exhibits an improved side effect profile to ABT-594 across a range of preclinical models. A 3.5-fold decrease in emetic liability for ABT-259 has been established in ferret, dog, and monkey studies. In a mouse model of seizure liability, ABT-259 was 8-fold less potent than ABT-594 to elicit seizures, which suggests that ABT-259 may be safer for an i.v. formulation. In a model of GI motility, ABT-259 was devoid of activity at doses up to 16-fold above the antinociceptive dose, whereas ABT-594 exhibited statistically significant effects at a dose three-fold above the antinociceptive dose.

At the *in vitro* level, ABT-259 and ABT-594 are very similar, but not identical. Whereas radioligand binding profiles for ABT-259 and ABT-594 are nearly indistinguishable, ABT-259 exhibits a six-fold decrease in functional activity at the ganglionic nicotinic acetylcholine receptor (nAChR). The significance of this finding relates to the established role of activation of ganglionic nAChRs in the cardiovascular and gastrointestinal effects of nAChR agonists.

Mechanistic studies support a predominantly central nAChR-mediated mechanism of action for ABT-259. The antinociceptive activity of ABT-259 was fully blocked by i.c.v. administration of the nAChR antagonist, chlorisondamine in models of acute and persistent pain. By contrast, the antinociceptive effects in these models were not blocked by opioid antagonists. Evidence also exists to support additional non-CNS sites of action for ABT-259. Both ABT-594 and ABT-259 inhibited the *in vitro* release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP), at the level of the dorsal horn of the spinal cord, suggesting that both compounds can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes. These studies suggest that ABT-259 elicits antinociception predominantly by centrally mediated descending inhibitory pathways, but additional peripheral and/or spinal mechanisms may contribute the antinociceptive activity of this compound.

In summary, ABT-259 is fully efficacious in models of acute, persistent inflammatory, and neuropathic pain with nearly identical potency to ABT-594. ABT-259 exhibits between 3.5 and 8 fold improvements in therapeutic index relative to ABT-594 in models of emesis, seizure liability and acute toxicity. -

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## II. TRANSITION STRATEGY

The first ABT-259 transition team meeting was held on 10/30/98. Representatives from Discovery, Toxicology, Regulatory, New Product Development, Drug Analysis, Pharmacokinetics, Drug Metabolism, Process Research, PARD, CAPD, AI and the Venture were present. The ultimate transition team goal that was agreed upon during this meeting was to provide a therapeutic window for ABT-259 vs. that of ABT-594. With this goal in mind, the team decided that both safety and efficacy would need to be established and compared to ABT-594. The team agreed that the safety and efficacy of ABT-259 could reasonably be compared to ABT-594 by conducting two clinical single dose studies.

The first study would be a rising single dose, first time in man study of ABT-259. Approximately 6 doses of ABT-259 would be evaluated. Once a single dose MTD is established, this dose, along with 1-2 lower doses would be used in a Phase II molar extraction study similar in design to ABT-594 study M97-772. Approximately 150-200 patients would be enrolled in this study, with the pace of enrollment contingent on the inclusion of fecund females. This molar extraction study would provide some estimate of the efficacy and therapeutic window of ABT-259 in relation to ABT-594.

Supportive preclinical studies as well as limited PARD and CAPD activities would be required prior to the initiation of human clinical studies, but would be kept at a minimum until it was decided to fully develop ABT-259. Toxicology work would be limited to completing two week rat and monkey, Ames, mouse lymphoma, in vitro cytogenetics and mouse micronucleus studies. Metabolism work would be kept to a minimum as well. Hepatocyte, protein binding and a rat ADME study would be initiated as soon as drug substance was made available. Preliminary reports for these preclinical studies were to be available 12/98 in support of first time in man 1/99. Process research (D-45L) was to make two deliveries of drug substance. The first delivery would be non GMP and would be used to support the preclinical work. The second delivery was to be manufactured under GMP conditions and would be sufficient to complete the clinical studies and required stability. PARD was not to work on formulation development with the exception of providing the "powder in a bottle" (PIB) formulation for clinical studies. The PIB formulation requires on site reconstitution by an unblinded pharmacist who would dissolve the drug substance with the addition of sterile water for injection.

This plan derived by the transition team requires limited funding for 1998 and 1999 (\$1.5 and 2.5 MM respectively) but does not allow for development in support areas. If a decision is made to fully develop ABT-259, there will be little to no drug substance on hand to support additional clinical studies. Once drug substance is available PARD would need to begin efforts on a solid dosage form. Supportive toxicology studies for the enrollment of fecund females and long term dosing in clinical trials would need to be

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ABBT 0020599

established. It is estimated that these activities may take up to 9 months to complete before further clinical development would be possible. The impact of such limited funding will be evaluated at future transition team meetings so that there will be minimal development delay should we decide to fully develop ABT-259.

### **III. TRANSITION PROGRAM**

#### **1. Bulk Drug Synthesis**

ABT-259 is prepared by a similar method to that originally developed for ABT-594. During the 3<sup>rd</sup> quarter of 1998, approximately 250 g of non-GMP drug and 550 g of GMP drug was delivered to satisfy the transition team needs for planned clinical and nonclinical studies.

In January 1999 it became clear that certain lots of ABT-259 (including the toxicology and clinical lots) gave a very weak positive result when subjected to the Ames test for mutagenicity. Experiments revealed that this effect could be reduced to tolerable levels for single dose clinical studies by further purification. Recrystallization of the clinical lot yielded 266 g of material which gave a negative (albeit slightly elevated) Ames response.

Current effort is focused on understanding the root cause of the Ames positive results. The current data strongly suggests that low residual levels of an intermediate are carried through resulting in a mutagenic impurity in the drug at levels of 0.03-0.1%. Confirmation of this hypothesis should be available in early 2<sup>nd</sup> quarter 1999. If confirmed, another lot of bulk drug will then be prepared to demonstrate that the Ames issues are controlled and to provide further drug for clinical studies (anticipated late 2<sup>nd</sup> quarter availability).

#### **2. Formulation Development**

The Phase I formulation is a powder. This formulation will be used for the single rising dose and single dose Molar Extraction Studies. The powder will be reconstituted at the clinical study site using sterile water for injection. Unit doses of 50.5 mg free base will be dispensed into vials and shipped to the clinical site for reconstitution.

Clinical supplies that have been manufactured will support the single rising dose study. Additional supplies will have to be manufactured to support other planned studies and will require the availability of additional drug substance.

No other formulation work is planned during the transition phase.

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**ABBT 0020600**



Analytical methods developed for the drug substance will be used for Phase I formulation testing and release.

### **3. Toxicology**

The toxicology program has been designed to provide the data required to support the Phase I clinical program (single rising dose and molar extraction studies). Toxicology studies conducted with ABT-259 include acute toxicity studies, 14-day repeat dose studies, and tests for genotoxicity.

#### **Acute Toxicity Studies**

Single dose toxicity studies were conducted with ABT-259 in rats and mice using the oral and intravenous routes of administration. These studies were all completed and reported.

#### **Repeat Dose Toxicity Studies**

Repeat dose oral toxicity studies of 14-day duration were conducted with ABT-259 in rats and monkeys. These studies were completed and reported.

#### **Genotoxicity Studies**

Ames assay, in vitro cytogenetics assay and mouse micronucleus assay were conducted with ABT-259. The Ames assay results showed that ABT-259 was negative in all bacterial strains except TA-1535. With TA-1535, an extremely weak, but reproducible, positive response was obtained in the presence of S9 activation only. This mutagenic response was demonstrated to be due to an impurity and not ABT-259. The impurity was successfully reduced by a recrystallization process, although a small amount may still be present.

In order to include women of childbearing age in the molar extraction study, the following reproductive studies have to be conducted during the transition plan:

#### **Pregnant Rat Range-Finding Study**

This study was initiated in 3/99. The results of this study will be available in 5/99 for dosage selection for the Segment II study in rats.

#### **Pregnant Rabbit Range-Finding Study**

This study will initiate in 4/99. The results of this study will be available at the end of 5/99 for dosage selection for the Segment II study in rabbits.

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**ABBT 0020601**

**Segment II Rat Study**

This study will initiate in 5/99. Preliminary results from this study will be available in 9/99 for preparation of the IND submission. Final report for this study will be submitted after the IND filing.

**Segment II Rabbit Study**

This study will initiate in early 6/99. Preliminary results from this study will be available in 9/99 for preparation of the IND submission. Final report for this study will be submitted after the IND filing.

This transition plan results in the 14-day repeat dose studies being the longest duration toxicology studies conducted during the entire transition process. Studies of  $\geq 1$  month duration will have to be conducted before initiation of multiple dose clinical trials. This transition plan will not allow an early determination of potential toxicity of ABT-259 in longer term studies (i.e. finding of basophilic foci in the 6-month rat study of ABT-594). Also, further studies on the impurity that is responsible for the positive Ames results is necessary if detectable amounts still present in future lots.

**4. Drug Analysis**

Two analytical methods are currently available for ABT-259. The first method uses pre-column derivatization of the analytes with a fluorescent label (NBD-F). Quantitative analysis by HPLC with fluorescent detection of the labeled analyte achieves a lower limit of quantitation of approximately 30 pg/mL of sampled plasma. This sensitivity is appropriate for clinical pharmacokinetic studies. The second method does not require derivatization and uses HPLC with single quadrupole mass spectrometric detection. The limit of quantitation for this method is approximately 2 ng/mL and is sufficient for toxicological studies. The LC-MS method provides both time and cost advantages when compared to the HPLC fluorescence detection method.

As was found with ABT-594, it is expected that a metabolite of ABT-259 is the carbamoyl glucuronide. It is also expected that this metabolite is easily hydrolyzed back to ABT-259 under alkaline conditions. Both ABT-259 and its carbamoyl glucuronide are expected to be found in human urine. Urinary excretion is expected to be the major route of elimination. In order to assess the urinary clearance of ABT-259 and its major metabolite, the sample preparation method for urine must account for the instability of ABT-259 carbamoyl glucuronide. In order to assure the specificity of the quantitative LC-MS method for ABT-259 from urine, it is estimated that approximately 100 mg of the carbamoyl glucuronide of ABT-259 would be required.

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ABBT 0020602

## 5. Pharmacokinetics

### Preclinical Pharmacokinetics of ABT-259

The pharmacokinetic behavior of Abbott-173259 was evaluated in CD-1 mice, Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. The pharmacokinetics of Abbott-173259 following a 200 nmol/kg (36.4 µg/kg) intravenous dose in mouse were characterized by a very short plasma elimination half life ( $t_{1/2}$  = 0.7 hours) and rapid plasma clearance ( $Cl_p$  = 3.7 L/hr·kg). The half life was approximately two-fold longer (1.4-1.9 hours) with a corresponding decrease in plasma clearance (0.7-1.2 L/hr·kg) in both rat and monkey following a 600 or 20 nmol/kg (109.3 or 3.6 µg/kg) intravenous dose, respectively. The longest half life and lowest clearance values were noted in the dog with mean values of 2.9 hours and 0.5 L/hr·kg, respectively following a 20 nmol/kg (3.6 µg/kg) intravenous dose. Volume of distribution values ( $V_b$ ) exceeded 2.1 L/kg in all species.

Abbott-173259 was rapidly absorbed from an aqueous solution following oral administration in both dog and mouse, with peak plasma concentrations observed within the first sixty minutes of drug administration. Absorption was slightly slower in the monkey and rat, with peak plasma concentrations noted 1.8-2.1 hours after oral dosing. Peak plasma concentrations averaged 4.66 and 3.22 ng/mL following a 100 nmol/kg (18.2 µg/kg) oral dose in monkey and dog, respectively. Abbott-173259 peak plasma concentrations averaged 10.47 and 12.89 ng/mL following a 200 or 600 nmol/kg (36.4 or 109.3 µg/kg) oral dose in mouse and rat, respectively. Bioavailability of Abbott-173259 following a single IP dose in mouse and rat averaged 80.1 and 60.6 percent, respectively. The oral bioavailability of Abbott-173259 from the aqueous solution formulation averaged 108.9, 60.3, 72.8 and 32.8 percent in the mouse, rat, monkey and dog, respectively.

Abbott-173259 peak concentrations and area under the curve values were approximately two-fold higher in the brain tissues and spinal cord following a 300 nmol/kg (54.7 µg/kg) oral dose in rat. The highest concentrations of parent drug were located in the brain stem with a peak tissue to plasma ratio of 2.4:1 following the oral dose. The Abbott-173259 half-life in brain tissues paralleled that described for the plasma with values of ~1.5-2.6 hours following an oral dose in rat.

The pharmacokinetic profiles of Abbott-173259 following 2, 5, 15 or 40 mg base/kg/day oral doses in rat were generally characterized by a low degree of animal to animal variability within each treatment group. No substantial differences were noted between the male and female subgroups nor between the values obtained at the beginning (Day

0) or end (Day 13) of the study. Within the small number of animals in each dose group, AUC values in the 2 (1008.9 ng•hr/ml) and 5 (2629.2 ng•hr/ml) mg base/kg/day treatment groups were proportional to the differences in dose. AUC values in the 15 (5698.8 ng•hr/ml) and 40 (17096.0 ng•hr/ml) mg base/kg/day treatment groups were lower than would have been predicted from the values in the 2 and 5 mg base/kg/day dose groups. A comparison of the area under the curve values derived from multiple dosing to that derived from a 0.6 µmol/kg single intravenous dose in a separate group of rats provided an estimate of 54.5, 64.6, 41.4 and 29.6 percent bioavailability in the 2, 5, 15 and 40 mg/kg/day dose groups on Day 0, respectively; bioavailability values averaged 59.9, 62.5, 45.1 and 50.8 percent in the same treatment groups on Day 13.

#### Preclinical Pharmacokinetics of ABT-259

The pharmacokinetics of ABT-259 were evaluated in mouse, rat, dog and monkey as single and multiple doses (rat and monkey only). As seen in the table below, the pharmacokinetic profile of ABT-259 in these animals was found to be very similar to that of ABT-594.

Preclinical Pharmacokinetics of ABT-594 vs. ABT-259					
Species		T <sub>1/2</sub> (h)	T <sub>max</sub> (h)	CL/F (L/h)	F (%)
Mouse	ABT-594	1.0	0.4	5.1	78
	ABT-259	1.5	0.4	3.4	100
Rat	ABT-594	2.0	1.5	2.8	61
	ABT-259	1.4	1.8	2.0	60
Dog	ABT-594	4.2	1.2	1.1	35
	ABT-259	1.5	0.8	1.6	33
Monkey	ABT-594	1.4	2.2	2.0	80
	ABT-259	1.9	2.1	1.0	73

In rat models for nociceptive pain, a minimum effective concentration of approximately 1 ng/mL was required for adequate pain relief. In rat, a dose of approximately 11 µg/kg produced a peak ABT-259 plasma concentrations of greater than 2 ng/mL, and plasma concentrations remained above 1 ng/mL for approximately 2 hours after dosing.

The allometric scaling of data from animals to humans suggests that ABT-259 is predicted to have a long elimination half-life of greater than 6 hours in humans with a clearance approximating 20 L/h and volume of distribution approximately 182 L. These values are very similar to the human pharmacokinetic parameters of ABT-594.

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**PK Activities during transition phase:**

- Evaluate PK of ABT-259 in Phase I single dose study.
- Write PK section of IND and update Clinical Brochure.
- Evaluate PK of ABT-259 in molar extraction study

**6. Metabolism Program**

In order to quickly generate metabolism and related data in support of the toxicology and clinical programs, several preliminary *in vivo* and *in vitro* studies have already been completed.

**Plasma Protein Binding.**

Initial *in vitro* studies have established that [<sup>3</sup>H]ABT-259 is poorly bound to plasma proteins, averaging 21.6% in rat plasma and 29.8% in human plasma.

***In Vivo* Metabolism in Rats.**

Preliminary metabolism studies conducted in bile duct-cannulated rats after a 20 µg/kg intraduodenal and intravenous dose of the radiolabeled drug indicated that the intraduodenal dose is rapidly and well absorbed. The majority of the radioactive dose (about 80 to 90%) is excreted into the urine after either route of administration; biliary and fecal excretion were minor. ABT-259 is not extensively metabolized in rats since unchanged parent drug accounted for about 70% of the AUC<sub>0-4</sub> for total plasma radioactivity and 72 to 82% of the dose in urine. Five minor unidentified metabolites were detected in plasma, urine and bile. At least one metabolite appears to be a glucuronide or sulfate conjugate of parent drug. Efforts are being made to isolate and characterize these components.

***In Vitro* Metabolism.**

Studies with liver microsomes indicate that the NADPH-dependent CYP mediated metabolism of ABT-259 is qualitatively similar in humans, rats and monkeys. A comparison between the data from two human liver microsomal preparations suggests a large inter-individual difference in oxidative metabolism (about 7-fold). However, since ABT-259 appears to be largely excreted in the urine as unchanged parent drug, it seems unlikely that inter-individual variability in oxidative metabolism would significantly impact the disposition of the drug in humans. Hepatocyte and liver slice incubations indicate that the monkeys will more extensively metabolize ABT-259 than either mice, rats or humans.

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### **Cytochrome P450 (CYP) Inhibition Studies.**

The effect of ABT-259 on isoform-specific CYP-dependent monooxygenase activities was examined in human liver microsomes. The results suggest that even at a concentration of 4  $\mu$ M, which is about 1000-fold higher than the projected clinically relevant concentration (4 nM), ABT-259 produced an average of <10% inhibition of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A activities. Hence, clinically significant drug-drug interactions due to ABT-259 inhibition of the metabolism of coadministered drugs metabolized by these CYP enzymes is considered unlikely.

## **7. Clinical**

### **Phase I Single Dose Design**

This is a first-in-man, single center, Phase I, randomized, double-blind, placebo-controlled study of single escalating doses of ABT-259 in healthy, adult, male volunteers. Approximately 60 subjects will be assigned to 6 groups of 10 (Groups 1-6). Test preparation will be randomly assigned such that seven (7) subjects receive ABT-259 alone and three (3) subjects will receive placebo. Groups 1-6 will be dosed sequentially with escalating doses of ABT-259. The doses chosen for the study are 100 ug, 200 ug, 400 g, 600 ug, 800 ug and 1000 ug.

Since ABT-594 was well tolerated up to a dose of 100 g given under fasting conditions, the objective of this study is to establish the tolerability of ABT-259 under fasting conditions. The results of this study will also be used to establish the starting dose for the molar extraction study in patients with acute pain after third molar extraction.

### **Objectives of Study:**

1. Assessment of the safety and tolerability of ABT-259.
2. Assessment of the pharmacokinetics of ABT-259.
3. Selection of doses for the molar extraction study in dental patients.

### **Decisions Based on Single-Dose Study Results**

At the completion of the Phase I single-dose study a decision of Go/No Go will be based on the safety, tolerability and pharmacokinetics of ABT-259. If the safety and tolerability of ABT-259 is better than that of ABT-594, with similar or better pharmacokinetic profile, ABT-259 will be dosed in the molar extraction study.

### **Phase II Molar Extraction Study**

In this study, patients will be treated with ABT-259 for the pain resulting from molar extraction surgery. The doses used in the molar extraction study will be based on the tolerated doses used in the Phase I single dose study.

#### **Objectives of the Study:**

1. Assess efficacy of ABT-259.
2. Assess safety and tolerability of ABT-259.
3. Assess pharmacokinetics of ABT-259.

## **IV. FUTURE DEVELOPMENT**

### **1. Bulk Drug Development-CAPD**

The following are a list of key activities which are necessary to complete bulk drug development for ABT 259.

- Develop a commercial supplier for the 2-fluoro-5-hydroxy pyridine compound.
- Identify a commercial supplier for the bulk drug substance.
- Complete registration runs at the bulk drug supplier.
- Complete process validation runs at the bulk drug supplier.

ABT 259 process currently uses the BOC azetidine alcohol as a key intermediate step. This intermediate is also used in the ABT 594 process, therefore it will be possible to take advantage of the development work that has occurred plus eliminate the need to complete registration runs at the vendor's manufacturing site.

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ABBT 0020607

***The timeline to accomplish the above activities would be approximately 24 months. This is based upon the continued use of the BOC azetidine alcohol as the key intermediate in the ABT 259 process. If an alternate process is needed then a longer development time would be required.***

## **2. Formulation Development**

Once a decision to develop a solid dosage form is reached it will take about 6 months to go through the process of identifying a solid dose that could be used in Phase II studies. A dose range would have to be identified in order to start work on the solid dosage form. The knowledge gained from ABT-594 should be applicable to this formulation development task. However, the challenges of low dosage strength and associated content uniformity continue to exist. The choice of excipients may also be limited based on data from ABT-594 compatibility experiments where several common excipients were found to be incompatible with the drug substance. The determination of related substances in a low dosage strength formulation will continue to present challenges to the analytical methodology.

## **3. Toxicology**

A list of planned toxicology studies and timing of these studies are as follows:

<b>Study</b>	<b>Start Date</b>	<b>Completion Date</b>
Mouse Lymphoma	7/00	12/00
1-Month Rat	7/00	1/01
1-Month Monkey	7/00	1/01
Mouse Range-finding	7/00	11/00
3-Month Rat	11/00	7/01
3-Month Monkey	11/00	7/01
3-Month Mouse MTD	11/00	7/01
Segment I Rat	5/01	12/01
Segment III Rat	5/01	2/02
6-Month Rat	6/01	6/02
1-Year Monkey	6/01	12/02
2-Year Rat CA	12/01	12/04
2-Year Mouse CA	12/01	12/04

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Assuming availability of bulk drug, this plan will allow us to initiate carcinogenicity studies

ABT 259 process currently uses the BOC azetidine alcohol as a key intermediate step. This intermediate is also used in the ABT 594 process, therefore it will be possible to take advantage of the development work that has occurred plus eliminate the need to complete registration runs at the vendor's manufacturing site.

The timeline to accomplish the above activities would be approximately 24 months. This is based upon the continued use of the BOC azetidine alcohol as the key intermediate in the ABT 259 process. If an alternate process is needed then a longer development time would be required.

#### **4. Drug Analysis**

The drug analysis department (D46W) will receive new triple quadrupole mass spectrometry instrumentation in April. The single quadrupole LC-MS method will be modified for use with the triple quadrupole instrumentation. Preliminary results indicate that the new instrumentation with the adapted method provides the sensitivity required to assay samples from clinical pharmacokinetic studies. The triple quadrupole LC-MS method simplifies the sample preparation procedure and will retain the time and cost efficiencies of the single quadrupole LC-MS method.

#### **5. Pharmacokinetics**

##### **PK Activities after transition phase:**

- All other standard Phase I studies including multiple dose, special population, bio/food effect, drug-interaction studies, etc.

#### **6. Metabolism**

At the present time, sufficient metabolism data are available for an IND filing. However, if a GO decision is reached, a number of additional standard studies will be necessary for an NDA filing. These include: 1) plasma protein binding studies in five species, 2) site of binding and human red cell penetration, 2) ADME studies in rats, mice and monkeys, 3) CYP characterization studies, 4) a tissue distribution in Sprague Dawley and Long Evans rats and 5) a radiolabeled ADME study in normal human subjects. Some of these studies could be initiated as early as 6/00.

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**7. Clinical**

**V. RISK ASSESSMENT/KEY ISSUES**

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**ABBT 0020610**

## **VI. TIMELINES MILESTONES**

1.

2.

## **VII. DEVELOPMENT COSTS**

1. Transition Program


2. Future Development

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**ABBT 0020611**

## **Meyer Deposition Exhibit 12**

**P's Exhibit EN**

 Bruce  
McCarthy /LAKE/PPRD/  
ABBOTT  
02/02/2001 02:33 PM

To Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Michael  
K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H  
Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, James  
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Steve C  
Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, Keith F  
Hendricks/LAKE/AI/ABBOTT@ABBOTT, Rosemarie K  
Waleska/LAKE/PPD/ABBOTT@ABBOTT, John M  
Leonard/LAKE/PPRD/ABBOTT@ABBOTT  
bcc  
Subject DSG

Liz-

Per our preliminary discussions regarding the DSG process for ABT-594 Go/No Go, here is a preliminary list of core team members (see below). Please comment on the number of core team members, as you have a better perspective on how many is too many (understanding that additional project team members will be involved whenever necessary). In addition, please comment on whether the list is sufficiently comprehensive.

When we discuss scope and frame during our first meeting, we will want to discuss several issues that came up at today's Leiden meeting (though I think these are not necessarily new):

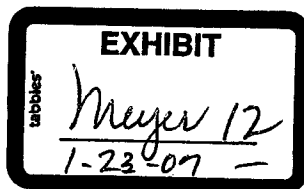
1. Given the results of Phase IIb, what is the value of the currently identified back-ups (ie, go to back up, proceed with 594 + start back up, etc...we can steal these analyses from the SDG project 2 years ago!)?
2. What additional work should be performed to understand time to onset issues (e.g., should additional work be performed in advance of the start of phase IIb, including perhaps the development of a parenteral formulation to better understand this issue) and what actions might we take based upon the results of this additional work?
3. How does ABT-594 fit in with a comprehensive strategy to bring NNR's for pain to the market? What kind of investment should be made to achieve success for this strategy (e.g., how many back-ups should be brought forward, when, what properties should the compounds have, how many simultaneously to clinic, etc). This issue is (obviously) very large, however, my impression is that this larger strategy needs to be formulated in order to have a go/no-go discussion about ABT-594. The issue also begs for a comprehensive pain strategy at Abbott (I think this latter point is unlikely to be achieved by our analysis, but we could always try to develop one nonetheless).

After we have a final core team list, let me know how I can help to get the first meeting scheduled ASAP. As we discussed at the preliminary meeting, we look forward to your expertise in facilitating this process (DSG as powerful decision-making tool), but we (members of the discovery/development/commercial team and especially those of us in the venture) very much want to take a leadership position in driving the overall process.

Venture/Development  
Marleen Verlinden  
Chris Silber  
Bruce McCarthy  
Mike Biarnesen

Discovery  
Jim Sullivan

Confidential



ABBT314925

Mike Meyer

Regulatory

Jim Steck/David Ross (Jim and David could back each other up)

Nigel Livesey

NPD

Laura Robinson/Rose Waleska (Laura and Rose could back each other up)

PARD

Howard Cheskin

PK

Walid Awni

Stats


David Morris/Jim Thomas

Thanks!

Bruce.

## **Meyer Deposition Exhibit 13**

**P's Exhibit EP**

 **Bruce McCarthy /LAKE/PPRD/ABBOTT**  
OTT  
02/19/2001 08:56 AM

Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT,  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT,  
Michael K Blamesen/LAKE/PPRD/ABBOTT@ABBOTT,  
James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael  
D Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Walid  
Awri/LAKE/PPRD/ABBOTT@ABBOTT, Richard G  
Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C  
Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H  
Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, David D  
Morris/LAKE/PPRD/ABBOTT@ABBOTT, Howard S  
Cheskin/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject Scientific Strategy for ABT-594/NNR Tolerability

Please note the Scientific Strategy for ABT-594/NNR Tolerability Meeting to take place tomorrow. This meeting is a follow-on to the Leiden review, in which a recommendation was heard for a comprehensive strategy to address tolerability issues related to NNRs for pain, including ABT-594 and follow-ons. The meeting is intended to initiate a process of planning and execution to improve tolerability via all available avenues, including (but not limited to): generation of more selective follow-on compounds, follow-on compounds with different pharmacokinetics, pharmaceutical and/or dosing manipulation of ABT-594, etc. Any strategies to improve the tolerability of NNRs for pain would be directed by a scientific basis for the tolerability concerns.

This first meeting is intended to brainstorm how we might approach this issue. We should begin to define issues, scope, vision, potential plans of action, etc. In the near future, we should clarify our strategy and document it. In addition, we'll need to develop a timeline for execution.

Please come prepared with your ideas on tolerability issues. I have attached an agenda.

See you tomorrow!  
Bruce.



Tolerability21901.doc

----- Forwarded by Bruce McCarthy/LAKE/PPRD/ABBOTT on 02/19/2001 08:41 AM

#### Calendar Entry

☐ Appointment ☒ Invitation ☐ Event ☐ Reminder ☐ Anniversary

Brief description:

Scientific Strategy for ABT-594/NNR Tolerability - Analgesia Venture Conf Room - w/Lunch

Date:

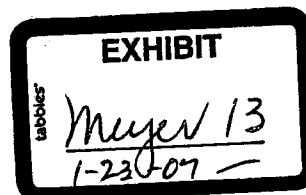
02/20/2001

Time:

11:00 AM - 12:30 PM

Detailed description:

Invitations have been sent to: Bruce McCarthy/LAKE/PPRD/ABBOTT, Christopher J Silber/LAKE/PPRD/ABBOTT, Michael K Blamesen/LAKE/PPRD/ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT, Michael D Meyer/LAKE/PPRD/ABBOTT, Walid Awri/LAKE/PPRD/ABBOTT, Richard G Granneman/LAKE/PPRD/ABBOTT, Kennan C



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ABBT0115991



Marsh/LAKE/PPRD/ABBOTT, Marleen H Verlinden/LAKE/PPRD/ABBOTT, David D  
Morris/LAKE/PPRD/ABBOTT, Howard S Cheskin/LAKE/PPRD/ABBOTT

---

Chairperson: Nancy M Palticke/LAKE/PPRD/ABBOTT  
This meeting repeats starting on (if the date occurs on a weekend the meeting).

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ABT-594 Tolerability Brainstorm Discussion  
Agenda  
February 19, 2001

1. Brief Review of Tolerability Issues to date
2. Individual perspectives on issues and questions related improving tolerability  
Sullivan/Meyer/Marsh  
  
Awni/Granneman  
  
Cheskin  
  
Morris  
  
McCarthy
2. Begin to define scope and vision, prioritize issues and questions and identify prerequisites
3. Define Next Steps, including potential processes (e.g. analyses, discussions, consultations, trials, etc) to solve/answer prioritized issues and questions

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Created on 2/19/2001 8:34:00 AM

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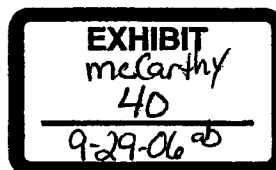
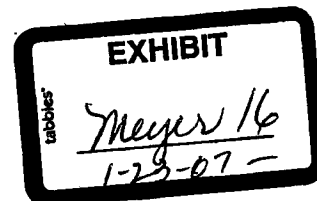
# **Meyer Deposition Exhibit 16**

**P's Exhibit EV**

GLOBAL  
PHARMACEUTICAL  
DISCOVERY

INTERNAL REVIEW  
MARCH 2001

Book #27  
Michael Meyer  
D-47W, AP9A-3



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ABBT 0024132

Project Leader: Michael Meyer  
 Chemistry: William Bunnelle  
 Biology: Carol Surowy  
 Commercial: Laura Robinson

**Neuronal Nicotinic Receptor Project:  
 ABT-594 Backup for Pain**

DDC target date: 2001

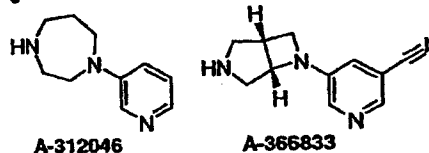
The primary objective of the Neuronal Nicotinic Receptor (NNR) project is to identify a structurally distinct follow-on to ABT-594 for use as a non-opioid, non-NSAID analgesic for the treatment of acute, chronic and neuropathic pain. The targeted compound should exhibit a comparable spectrum of analgesic activity to ABT-594 as assessed by existing preclinical models, and exhibit a minimum ten-fold, and ideally 30-fold improvement in therapeutic index with respect to emetic liability.

During the past year, the project has continued to focus on a mechanism-based approach to the identification of compounds exhibiting retention of broad-spectrum analgesic activity associated with ABT-594, but with an improved therapeutic index relative to the key adverse events of emesis, nausea, and dizziness that have consistently been observed during the clinical evaluation of ABT-594. ABT-594 is currently completing a Phase IIb trial in diabetic neuropathy at doses up to four fold above the doses studied in the previous neuropathic pain trial, with results from that trial expected by May 2001. It will be critical to the continuation of the program to demonstrate enhanced clinical efficacy at these higher doses. Beyond this important milestone, the program is faced with two additional key issues: are efficacy and side effects governed by distinct and separable NNR subtypes, and can preclinical models accurately predict the improved therapeutic index required in an ABT-594 backup?

The preponderance of evidence continues to support the hypothesis that activation of  $\alpha 4$  subunit-containing NNR subtypes is required for analgesic efficacy, and that activation of  $\alpha 3$  subunit-containing NNRs is associated with emetic liability. Previously, detailed studies both within the project<sup>1</sup> and outside of Abbott<sup>2</sup> have provided convincing support for the role of central  $\alpha 4$  subunits in the mediation antinociception in models of acute thermal pain. Additional work within the last six months has extended these studies to models of persistent inflammatory and neuropathic pain. Whereas these studies have begun to implicate the involvement of peripheral sites as well as central sites of action, these studies continue to support the importance of  $\alpha 4$  subunit-containing NNRs from both the central and peripheral sites. Since the initiation of the NeuroSearch collaboration in January 2000, the project has screened all new and many historical compounds against human recombinant NNR subunit combinations. This data set has allowed further correlation of emetic liability to activation of the  $\alpha 3$  NNR subunit.

The project team has relied on the ferret emesis model to predict emetic and nausea liability, and general models of balance, coordination, and CNS-related toxicities as indicators of improvement in therapeutic index that may or may not correlate to the adverse event of dizziness reported for ABT-594. Using established models of efficacy, and these models of side effect liability, the project team has identified two compounds—A-312046 and A-366833—that exhibit a significantly improved therapeutic index across these models. The in vivo profile of A-312046 suggests particular utility in the treatment of neuropathic pain, but this compound suffers from poor bioavailability in two of three species examined. Transdermal and prodrug approaches are currently being explored. A-366833 exhibits efficacy across all pain models tested to date, has excellent bioavailability, and a 20 to 30-fold improvement in therapeutic index vs. ABT-594. Both A-312046 and A-366833 exhibit significantly improved selectivity for  $\alpha 4$ -containing NNR subtypes vs.  $\alpha 3$ , and both validate the viability of the molecular approach to the identification of follow-on compounds to ABT-594.

Figure 1. Structures of Best Leads



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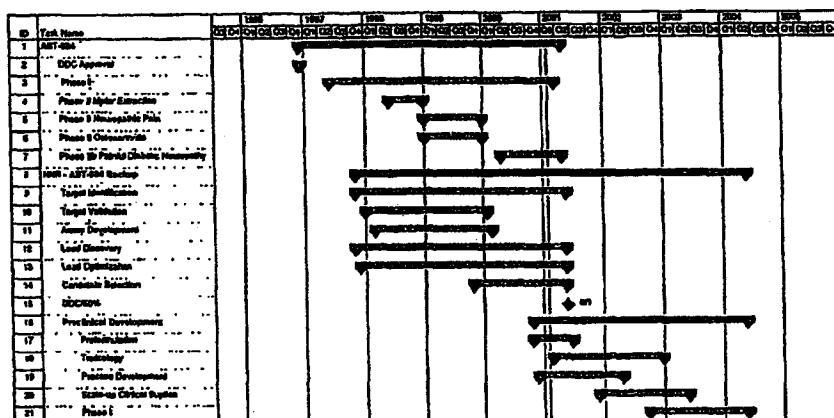
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6668-R2

Neurological and Urological Diseases Research  
1001Discovery Project Review  
NNRs - ABT-594 Backup  
2**Timelines****SWOT Analysis:****Strengths (technical and commercial factors)**

- Novel mechanism and broad-spectrum of analgesic activity observed in preclinical models offers differentiation from other analgesics.
- ABT-594 has established proof of principle for both nociceptive and neuropathic pain states.
- Abbott has established a leadership position in the preclinical and clinical evaluation of NNRs for the treatment of pain.
- Abbott has established a six-year research collaboration with NeuroSearch (Denmark) that has provided access to several novel structural classes and has made available the human recombinant NNR subtypes as a screening tool.
- Efficacy in both nociceptive and neuropathic pain would differentiate compound from current therapies.
- Novel mechanism provides potential for use as monotherapy or in combination with an opioid or other MOI product (opioid-sparing regimens).
- Potential to complement oncology franchise as analgesic therapy for cancer pain.
- PPD building GP relationships in pain management with Mobic, and has strong relationships with Neurologists (neuropathic pain and migraine) through Depakote.

**Weaknesses (technical and commercial factors)**

- Although newer compounds emerging from the project demonstrate comparable efficacy to ABT-594 with a decreased side effect liability as assessed in preclinical models, the degree to which these improvements will be realized clinically is unknown.
- The factors that prevent rapid absorption of ABT-594 in humans and thus limit the usefulness of ABT-594 for the treatment of acute pain have not been determined, and thus not resolved by potential backup compounds.
- The clinically relevant side effect of dizziness has no identified preclinical correlate, and cannot be directly addressed in the preclinical characterization of potential backup compounds.
- The correlation between in vitro profile and in vivo efficacy and safety profile is limited. Whereas lack of in vitro selectivity invariably translates into a poor therapeutic index, good selectivity does not guarantee an improved TI.

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ABBT 0024134

Neurological and Urological Diseases Research  
1Q01

Discovery Project Review  
NNRs - ABT-594 Backup  
3

#### Opportunities (commercial and competitive factors)

- Analgesia represents a very large market with significant unmet need, yet no novel class of analgesic exhibiting a new mechanism of action has emerged in the last fifty years.
- Need exists for agents with efficacy superior to COX-2s without the side-effect and dependence liability of opioids for treatment of nociceptive pain; opportunity is primarily in the oral segment.
- For neuropathic pain, need exists for oral therapies with superior pain relief, increased responder rates, and lower side-effects than the gold standard tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs).

#### Threats (commercial and competitive factors)

- Increasing competition from major pharmaceutical companies (e.g., SIBIA/Lilly, Aventis/Targacept, Novartis, Pharmacia, Johnson and Johnson); risk that another NNR may be first to market.
- COX-2s have raised the hurdle for treatment of chronic mild-moderate pain (especially OA and RA), and will dominate this market.
- Superior efficacy will be important to penetrate "moderate-severe" pain market.
- Pregabalin (currently Ph III) likely to have a neuropathic pain claim, and has the potential to raise the bar regarding efficacy and/or AE profile (Note: ongoing Ph III trials have very recently been halted due to toxicology finding in mice).
- Potential for negative public perception regarding nicotinic mechanism; public education and CME will be critical to lay the foundation for a successful launch

#### Market Overview

##### New or Target Specific Market Issues

Total worldwide sales of prescription analgesics in 2000 were approximately \$12.9 billion. NSAIDs represent the largest sales share by class, followed by non-narcotics, narcotics, and adjuvant analgesics (AEDs and TCAs). U.S. prescription pain sales were \$7.9 billion, an 18% growth over 1999, fueled by strong growth of Celebrex and Vioxx. In the US, COX-2s are replacing traditional prescription NSAIDs, and increasing the size of the Rx market due to switching from OTC products. Sales of the COX-2s grew from \$1.5B in 1999 to \$3.0B in 2000. The US neuropathic pain market is approximately \$500MM, and is driven by continued growth of off-label Neurontin usage in neuropathic pain (\$210MM in 1999 growing to \$350MM in 2000, factored for use in pain).

Ex-US prescription pain sales were approximately \$5.0 billion in 2000, with growth of 9% over 1999 sales. Ex-US uptake of the COX-2 inhibitors has been much slower, due to premium pricing vs. traditional NSAIDs, an average of one year launch delay vs. the US in major European markets, and no launch in Japan. However, EX-US sales of COX-2s has grown significantly, from \$100MM in 1999 to \$350MM in 2000. The ex-US neuropathic pain market is approximately \$300MM. Neurontin sales are only a fraction of US sales (estimate only \$60MM for usage in pain), with carbamazepine remaining the gold standard for neuropathic pain. Neurontin has not launched in Japan.

Growth of the neuropathic pain market will be driven by increasing prevalence of diabetes, and a growing elderly population will increase incidence of numerous disorders, including herpes zoster and stroke, which often lead to neuropathic pain. In addition, diagnosis is expected to increase as physicians and patients become better educated regarding neuropathic pain, and more effective and tolerable medications become available. The nociceptive pain market is also expected to grow due to increasing prevalence of OA and RA in an aging population and more aggressive usage of analgesics.

Significant unmet need remains in the treatment of both neuropathic and nociceptive pain (Figures 2 and 3). There are no highly efficacious treatments for neuropathic pain. A new agent that exhibited superior efficacy, even in the absence of an improved side effect profile, would constitute a therapeutic advancement. Although the nociceptive pain market is better served, only the opioids exhibit efficacy in the treatment of severe pain. An agent with the efficacy of an opioid with decreased side effect liability relative to an opioid would constitute a therapeutic advancement.

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Figure 2. Unmet Needs: Treatment of Neuropathic Pain

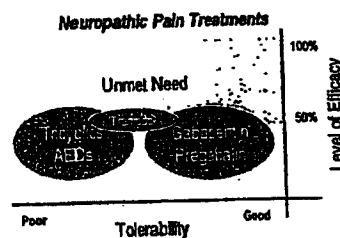
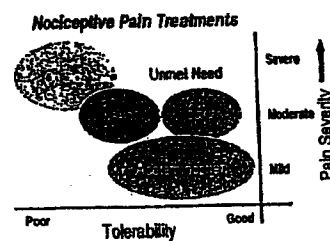


Figure 3. Unmet Needs: Treatment of Nociceptive Pain

Target Product Profile

Basis of Profile: Previous marketing research for ABT-594 PPCC, as well as follow-on qualitative and quantitative marketing research in analgesia.

Clinical Attributes/Probability	Preclinical Correlates
<ul style="list-style-type: none"> <li>Efficacy in neuropathic pain superior to gold standards (increase pain relief and/or increase responder rates)</li> <li>Efficacy in moderate to severe nociceptive pain</li> <li>Non-scheduled</li> <li>Onset of action within 30-45 minutes</li> <li>No tolerance, dependence or abuse potential</li> <li>Favorable safety profile</li> <li>Frequency of dosing no greater than BID</li> <li>No significant drug interactions</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy superior to gabapentin or pregabalin in Chung model of neuropathic pain</li> <li>Efficacy comparable to superior to NSAIDs in nociceptive pain models</li> <li>Lack of drug reinforcing properties</li> <li><math>T_{max} &lt; 30</math> min after oral administration in preclinical models</li> <li>Retains efficacy upon repeated administration, does not produce self administration in rodents</li> <li>Therapeutic index 10 to 30 fold greater than ABT-594</li> <li>Predicted human clearance comparable to or better than ABT-594</li> <li>Limited metabolism, clearance as parent drug</li> </ul>

Development Challenges

The emerging clinical profile of ABT-594 has significantly limited the potential market from the preclinical promise of efficacy in all pain states to a more limited scope of the treatment of neuropathic pain. Slow absorption and slow onset of analgesic effect plus significant adverse events of emesis, nausea, and dizziness have precluded ABT-594 from the large and lucrative acute pain and pain associated with osteoarthritis markets. There is, however, significant unmet need for the treatment of neuropathic pain; the existing drugs are minimally efficacious and the side effect profile is poor. In order to fully exploit the potential of the NNR pharmacology platform for the treatment of pain, compounds with significantly greater tolerability are required. The issue of rapid onset may not be an issue per se, but may only be an issue with ABT-594 as a result of being unable to dose at a sufficient level to achieve therapeutic plasma concentrations at early time points prior to  $T_{max}$ . The regulatory pathway for an indication in the treatment of neuropathic pain is much less well established than for the treatment of pain associated with osteoarthritis, and this will remain a development challenge for both ABT-594 and additional follow-on compounds.

The development paradigm adopted for ABT-594 needs to be challenged as backup compounds are brought forth for development. The assumption that solution dosing would provide a rapid answer as to the viability of NNR pharmacology for the treatment of pain resulted in incorrect conclusions as to the tolerability of ABT-594, and consequently resulted in a slowing down rather than an acceleration of the development program. Although third molar extraction was a logical starting point to evaluate ABT-594, this is a model that is optimized for evaluation of NSAIDs and not necessarily the most appropriate model for the evaluation of a novel pharmacology.

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5**SECRET - 2010 02 22 10:10:10****Background**

Although preclinical data from nicotine, and more recently from epibatidine, have been in existence for many years supporting the potential analgesic activity of NNR agonists, no clinical results unequivocally supporting a role for this novel pharmacology in the treatment of pain have emerged. ABT-594 has changed that situation. Clinical efficacy in trials of molar extraction, osteoarthritis, and neuropathic pain achieved with ABT-594 has validated the NNR approach to the treatment of pain, and Abbott alone is in possession of this information. ABT-594, however, is an imperfect drug. Effects were only modest at the maximum dose of 75 µg B.I.D., and the full potential of this pharmacology will be more clearly revealed when the results of the ongoing clinical trial in painful diabetic neuropathy (at doses of 150, 225, and 300 µg B.I.D.) become available. Dose-limiting side effects of emesis, nausea and dizziness have made it difficult to reach what we believe should be therapeutically relevant plasma concentrations of ABT-594 required to achieve maximal efficacy. Hence, the challenge facing the project team is to maintain the broad-spectrum analgesic efficacy of ABT-594 across models of acute, persistent and neuropathic pain while decreasing side effect liability, particularly in models of emesis.

**Drug Target**

Previously, the project team and outside investigators have provided strong evidence for the involvement of the  $\alpha 4$  and  $\beta 2$  NNR subtypes in the mediation of nociception in models of acute thermal pain<sup>1-4</sup>. Both  $\alpha 4^{+/-}$  and  $\beta 2^{+/-}$  knockout studies, as well as antisense studies have strongly implicated the  $\alpha 4\beta 2$  NNR subtype in the modulation of acute antinociception. More recently, the project team has begun investigation of the differences and similarities between NNR mechanisms in acute models vs. mechanisms in models of persistent inflammatory and neuropathic pain. These ongoing studies confirm the involvement of supraspinal sites and the activation of descending inhibitory pathways, but also now implicate additional peripheral sites of action. In particular, in the Chung neuropathic pain models, sites within the vicinity of the dorsal root ganglia (DRG) cell bodies have been implicated as an important peripheral site of action for NNRs. Preliminary results suggest the involvement of the  $\alpha 4\beta 2$  subtype at these sites as well. Access to human recombinant NNR clones through the NeuroSearch agreement has made it possible to further refine the relationship between activity at the  $\alpha 3\beta 4$  NNR subtype and emesis liability. These results continue to support a clear link between activity at this subtype and emetic liability (see Progress to Date).

**Genomic Profile**

There is a growing body of evidence to suggest genetically mediated differences both in the perception of pain and the effects of analgesics in the treatment of pain<sup>5,6</sup>. Mogil (Univ. of IL) has reported studies on the genetic variability across inbred strains of mice both to pain perception and the effects of various analgesics in numerous pain models<sup>7-10</sup>. Flores (Univ. of Texas) has recently demonstrated significant variability of NNR-mediated antinociception across various mouse strains<sup>11</sup>. In several instances, human disease states have been linked to genetic abnormalities of NNR subunits. Mutations of the  $\alpha 4$  subunit have been linked to autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)<sup>12-14</sup>, and mutations of the  $\alpha 7$  subunit have been linked to auditory gating deficits among schizophrenics and their immediate relatives<sup>15,16</sup>.

**Uncertainties, Assumptions and Hurdles**

- It has been assumed that the modest efficacy observed to date clinically with ABT-594 is a result of under-dosing, and this assumption is supported by an analysis of plasma levels achieved clinically relative to plasma levels required to produce efficacy in preclinical models. The ongoing Phase IIb trial in painful diabetic neuropathy will resolve this uncertainty.
- The degree to which preclinical models can predict adverse event liability associated with ABT-594 and resulting follow-on compounds is limited. Whereas the ferret emesis model is a well-established and quantitative model, nausea can be judged only qualitatively and no validated models of dizziness have been established. The project team has operated on the premise that measurable effects on balance, coordination and muscle strength will be a suitable surrogate marker for clinical dizziness, an assumption that may or may not be true.
- The project team's approach to the identification of compounds with improved therapeutic index is based on optimization of selectivity for the  $\alpha 4$ -containing NNR subtypes in vitro. Although not all compounds that exhibit selectivity for the  $\alpha 4$ -containing subtypes exhibit efficacy with decreased emetic liability, it is certainly true that failure to achieve selectivity invariably results in compounds exhibiting no significant improvement in therapeutic index relative to ABT-594. At present,

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- there is no clear SAR pathway to compounds exhibiting complete specificity for the  $\alpha 4$ -containing NNR subtypes. In addition, there may be theoretical limits to the degree to which efficacy and side effect can be separated.
- The "ideal profile" required of an NNR modulator for the treatment of pain remains uncertain. The identification of compounds like A-366833 (see Properties of Lead Compounds) challenges the conventional wisdom that only compounds exhibiting full agonist activity (as measured by FLIPR assays) would be fully efficacious in pain models.

#### Abbott Insights and Competencies

Abbott is currently an industry leader in the field of nicotinic receptor research. Specifics of this competitive advantage include:

- Clinical proof of principle for the treatment of pain.
- Established collaboration with NeuroSearch, offering a significant expansion of the compound library and an opportunity to resume screening against human recombinant NNR subtypes.
- State-of-the-art behavioral models for assessing analgesic potential of preclinical leads.
- Large library of potent NNR agonists exhibiting potent analgesic activity.
- Collaborations and relationships with key opinion leaders in pain as well as NNR biology and chemistry.

#### Key Achievements and Milestones

##### Achieved

- Established screening facility in Norway; stable cell lines expressing functional  $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 4\beta 4$ , and  $\alpha 3\beta 2$  NNR subtypes; generating data on all new project compounds (3Q/00).
- Identified lead series, including novel series of fused diazabicycloheptanes, exhibiting a 20 to 100 fold better separation between  $\alpha 4\beta 2$  and  $\alpha 3\beta 4$  subtypes than that seen with ABT-594 (4Q/00).
- Further established the link between efficacy at the  $\alpha 4\beta 2$  subtype and analgesic effect (4Q/00).
- Extended initial finding relating to the importance of the  $\alpha 4\beta 2$  subtype in acute thermal pain to additional models of nociceptive and neuropathic pain (4Q/00).

##### Not achieved

- Presentation of DDC backup candidate to ABT-594 (4Q/00).

##### 0-6 months

- Complete safety evaluation of A-366833 for DDC presentation (2Q/01).
- Complete evaluation of efficacy and emetic liability upon oral administration of A-366833 (1Q0/01).
- Identify prodrug analog of A-312046 that produces a 3-5 fold improvement in oral bioavailability in the dog (2Q/01).

##### 6-12 months

- Address the limitations of ABT-594 for the treatment of acute moderate to moderately severe pain (4Q/01).

#### Cholinergic Channel Approach

Termination of the cholinergic channel approach for the treatment of pain would be subject to the following:

##### 0-12 months

- No improvement in efficacy at doses of 300  $\mu$ g BID in diabetic neuropathy trial vs. initial 75  $\mu$ g BID trial (2Q/01)
- Mechanism based tolerance is observed clinically following higher doses (2Q/00)
- Inability to identify compound with comparable T.I. to A-366833 meeting all safety requirements for DDC approval (4Q/01).

##### 1+ year

- Physical dependence is observed clinically

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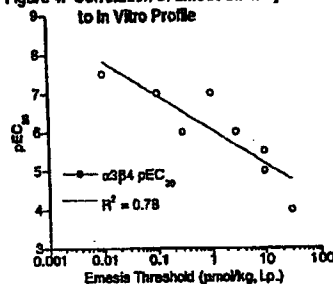
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7**Progress to Date****Biological Advances****Correlation of Analgesic Efficacy or Emesis to NNR Subtypes**

A strategy to use correlation to in vitro profile to identify NNR agonists that demonstrate analgesic activity with significantly reduced side effects has been pursued to identify a backup for ABT-594. The approach is based on our research, as well as that of others, which has revealed that activation of  $\alpha 4$ -containing, particularly  $\alpha 4\beta 2$ , NNR subtypes play a significant role in the antinociceptive properties of nicotine and related compounds, whereas other subtypes, e.g.,  $\alpha 3\beta 4$  NNRs, have been linked to some of the adverse (e.g. gastrointestinal and cardiovascular) side effects of NNR agonists. More recently, identification of novel compounds with greater NNR subtype selectivity within the project has provided significant support for this argument. We have found that compounds that show good agonist activity at  $\alpha 4\beta 2$ , but poor or less activity at  $\alpha 3\beta 4$ , show good analgesia together with reduced emesis and/or toxic side effects. To account for partial agonist activity and differences in oral bioavailability, Figure 4 correlates emesis threshold to  $EC_{50}$  (concentration required to produce 20% of the maximal effect of nicotine) values in the  $\alpha 3\beta 4$  cell line. Emesis is highly correlated to activation of the  $\alpha 3\beta 4$  subtype. On the other hand, compounds that show poor potency at  $\alpha 4\beta 2$  receptors, but good potency at  $\alpha 3\beta 4$ , tend to show a greater trend toward toxic side effects or emesis and are significantly less effective or ineffective at producing antinociception or antiallodynia in models of persistent or neuropathic pain. Certain highly  $\alpha 3\beta 4$ -selective compounds (e.g. A-333060) lacking any significant activity at the  $\alpha 4$ -containing subtypes are in fact hyperalgesic. Importantly, these correlations traverse several different series of compounds developed within the project. As subtype selectivity is an important issue in the identification of potential drug candidates with NNR activity, the project is continuing to make efforts to refine and strengthen these findings as it moves forward in the pain area, as well as in other potential target areas.

Figure 4. Correlation of Emetic Liability to In Vitro Profile

**Cloning and Expression of NNRs and Identification of Compounds with NNR Subtype Selectivity**

The NeuroSearch collaboration has allowed the Project to use cell lines expressing several of the different human NNRs to screen compounds for activity and subtype selectivity using FLUPR technology, in a relatively high throughput format. Human cDNAs for  $\alpha 4$ ,  $\alpha 3$ ,  $\beta 2$  and  $\beta 4$  were cloned in Norway at NeuroSearch during the first half of last year. During the 3Q 2000 NeuroSearch developed stable human cell lines (in HEK 293) expressing  $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 4\beta 4$  and  $\alpha 3\beta 2$ . Over the last 6 - 8 months these cell lines have been used at NeuroSearch to successfully screen all new compounds synthesized for the pain program here at Abbott, within the Project, and at NeuroSearch. The result has been the identification of a number of novel subtype-selective agonists, including those in new series such as one of the Project's current leads compounds (discussed below). The screening effort has also allowed us to increase our understanding of the NNR subtype profile, including effects of selectivity, potency, and efficacy, which may contribute to antinociception or antiallodynia.

In-house cloning efforts have focused on ferret receptors for  $\alpha 4$ ,  $\alpha 3$ ,  $\beta 2$  and  $\beta 4$ . Cloning of these cDNAs, which show good homology with the human receptors, is essentially complete. Stable cell lines expressing specific subtypes have been or are currently being developed and selected. As recent studies in the field continue to demonstrate increasing complexity to NNRs, use of recombinant receptors expressed in stable cell lines, transient expression of altered forms of the receptors, and studies using expression of the different subtypes in *Xenopus* oocytes (ongoing), will permit advances in our understanding of the distinct properties of these receptors. Initially these studies will provide: (i) greater insight into the correlation between subtype selectivity and effects observed in the ferret emesis model, and (ii) further understanding of the pharmacological and molecular properties of different NNR subtypes.

**Mechanistic Studies**

Both preclinical and clinical research indicate that the mechanisms underlying such pain states as acute, persistent or neuropathic pain can be quite different. Previous research in our project focused on the neuronal pathways and receptor subtypes that underlie NNR agonist-induced antinociception in a model of acute thermal pain. These studies demonstrated that NNR agonist-induced antinociception to acute thermal pain is mediated solely in the CNS and that antinociception to acute

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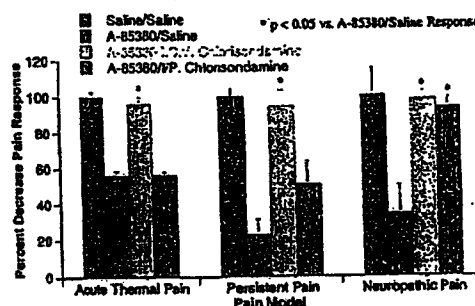
thermal pain occurs supraspinally. Use of selective receptor antagonists and antisense technology demonstrated the importance of the  $\alpha_4$  subunit in mediating NNR agonist-induced antinociception.

More recently we have examined the mechanism(s) of action in other pain states, i.e. persistent and neuropathic pain, in order to allow us to compare and contrast the manner through which NNR agonists are able to induce antinociception, analgesia and anti-allodynia. Due to its selectivity for NNR receptors, A-85380 was used as a prototypical agonist in these studies.

In order to examine the site(s) of NNR-mediated analgesic action in persistent pain, the ability of the NNR receptor antagonist chlorisondamine, a quaternary amine that does not cross the blood brain barrier, to alter A-85380-induced analgesia in the formalin model was assessed following systemic and central administration of the antagonist, which would induce peripheral and central blockade of NNR receptors, respectively. Centrally administered chlorisondamine blocked the analgesia induced by A-85380, whereas peripherally administered chlorisondamine only partially reduced A-85380-mediated analgesia, thus indicating a central site of action of NNR agonists as the major site in reduction of persistent pain.

A similar set of studies was performed to determine whether the anti-allodynia induced by A-85380 in the spinal ligation model of neuropathic pain was mediated either in the CNS or the PNS. In contrast to the acute and persistent pain models, both systemically and centrally administered chlorisondamine completely blocked A-85380-induced anti-allodynia. These findings were confirmed with another quaternary antagonist, hexamethonium, and another NNR agonist, A-312046, thus ruling out the possibility of nonspecific effects. Moreover, chlorisondamine given systemically did not alter A-85380-mediated antinociception in an acute thermal pain model, using neuropathic rats, strongly suggesting that the effect could not be accounted for by the antagonists crossing the blood-brain barrier through damage caused during the initial surgery to induce neuropathic pain. Thus both central and peripheral sites of action of NNR agonists appear to make major contributions to reducing neuropathic pain. Results from these series of experiments are summarized in Figure 5.

Figure 5. Effects of Central and Peripheral NNR Blockade in Models of Acute, Persistent and Neuropathic Pain



Studies to identify the location of NNR receptors underlying the peripheral site of anti-allodynic action have focused on the primary receptive field of the neuropathic pain, the plantar surface of the rat paw, and on the other major peripheral site, the dorsal root ganglia (DRG). A-85380-induced anti-allodynia was observed on injection into the primary receptive field, but showed greater potency upon injection into the contralateral paw, strongly suggesting a systemic effect. In contrast, A-85380 infused directly onto the DRG induced a dose-dependent anti-allodynia at doses that were ineffective when given systemically. The anti-allodynic effects of NNR agonists at the level of the DRG were replicated using epibatidine as the agonist, indicating that this effect is general to NNR agonists. Furthermore, the finding that nonspecific neuronal inhibition induced by infusing lidocaine directly onto the DRG did not induce anti-allodynia supported the selectivity of NNR action. In order to identify the NNR receptor subtype(s) that are mediating the anti-allodynic action of A-85380 in the DRG, the ability of pretreatment of the DRG with the nicotinic antagonists DH $\beta$ E, MLA, hexamethonium or mecamylamine to alter A-85380-induced anti-allodynia following DRG infusion has been assessed using at least one dose of each antagonist thus far. At 5 nmol, only DH $\beta$ E blocked A-85380 induced anti-allodynia whereas mecamylamine, hexamethonium and MLA had no significant effect. These results argue for a role for the  $\alpha_4\beta_2$  receptor subtype in mediating the peripheral action of A-85380 in reducing neuropathic pain. Further studies to confirm these novel findings are ongoing. The finding that a significant contribution to anti-allodynia/neuropathic pain by NNR agonists is made through a peripheral, as well as a central, site of action may suggest that good blood-brain barrier penetration need not be necessary for an NNR agonist to reduce neuropathic pain. A compound with this profile may offer an advantage by minimizing the potential of centrally mediated AEs such as dizziness, or possibly emesis.

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### Properties of Lead Compounds

Two compounds have emerged, A-312046 and A-366833, exhibiting pronounced improvements in therapeutic index relative to ABT-594 with retention of broad-spectrum analgesic efficacy across models of acute, persistent and neuropathic pain, and validate the concept that improved therapeutic index can be achieved via an enhancement in *in vitro* selectivity. A-312046, however, suffers from poor oral bioavailability in dog and monkey, and may require either a transdermal delivery or prodrug approach. A-366833 exhibits a further improvement over A-312046 relative to therapeutic index, achieves excellent oral bioavailability across three species, but preliminary cardiovascular evaluation has revealed a potential effects on QT interval prolongation.

#### *In Vitro* Profile:

In radioligand binding assays for the high-affinity nicotine-binding site from rat brain homogenate (predominantly  $\alpha 4 \beta 2$ ), A-312046 exhibited comparable affinity to ABT-594 (0.051 nM vs. 0.049 nM), while A-366833 exhibited significantly weaker affinity (3.12 nM). In CEREP screening assays, both compounds showed excellent selectivity for the nicotinic receptor.

In recombinant cell-based functional assays expressing the  $\alpha 4 \beta 2$ ,  $\alpha 3 \beta 2$ ,  $\alpha 3 \beta 4$ , and  $\alpha 4 \beta 4$  NNR subunit combinations, A-312046 exhibited approximately 4-fold weaker activity at  $\alpha 4$ -containing subtypes and 26-fold weaker activity at the  $\alpha 3 \beta 4$  subtype relative to ABT-594. Full, or nearly full agonist activity was retained across all subtypes. A-366833 exhibited a 100-300 fold weaker response (relative to ABT-594) at the  $\alpha 4$ -containing subtypes and maximal efficacy was less than 100%, but was nearly inactive at the  $\alpha 3 \beta 4$  subtype, exhibiting approximately 15% of the maximal efficacy of nicotine (See Table 1, Figure 7).

Figure 8. Structures of Best Leads

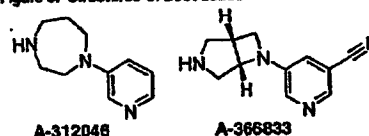


Table 1. *In Vitro* Profile of Most Promising Leads.

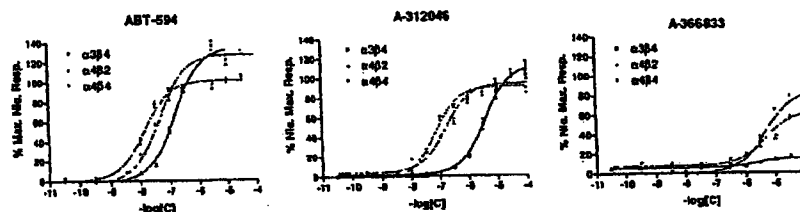
Compound	RLB* K <sub>i</sub> , nM $\alpha 4 \beta 2$ (Rat Brain)	Functional Response (EC <sub>50</sub> , $\mu$ M, % of Maximal Nicotine Response in parentheses)					
		$\alpha 4 \beta 2$ (Clonal)*	$\alpha 3 \beta 2$ (Clonal)	$\alpha 3 \beta 4$ (Clonal)*	$\alpha 4 \beta 4$ (Clonal)*	$\alpha 4 \beta 2 : \alpha 3 \beta 2$ 4 Sel. Ratio	$\alpha 4 \beta 2 : \alpha 3 \beta 4$ Sel. Ratio
ABT-594	0.049	0.046 (127%)	2.69 (111%)	0.16 (134%)	0.014 (100%)	3.5	11
A-312046	0.051	0.16 (95%)	27.5 (60%)	4.10 (119%)	0.064 (92%)	26	64
A-366833	3.12	4.6 (63%)	N.D.	(16%)*	4.7 (83%)	NC*	NC*
Epibatidine	0.042	0.036 (139%)	0.076 (129%)	0.015 (97%)	0.0085 (108%)	0.4	2

\* RLB = radioligand binding

\* Data from side-by-side comparison using human cell lines (NeuroSearch, Norway)

\* EC<sub>50</sub> not reliably calculable (NC) for agonists with maximal response below 20%

Figure 7. *In Vitro* Dose-Response curves for functional response at NNR subtypes.



#### *In vivo* Efficacy Profile:

Both A-312046 and A-366833 exhibit approximately comparable efficacy to ABT-594 across models of nociceptive (persistent and acute), neuropathic and visceral pain. The differences in *in vivo* potency are commensurate with the differences in potency observed *in vitro*. The relative potency in models of nociceptive and neuropathic pain differ for A-312046 and A-366833, with A-

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312046 exhibiting its best potency and efficacy in the neuropathic pain model, whereas A-366833 is most potent and efficacious in the persistent nociceptive pain model (Formalin model). Both compounds exhibit the broad-spectrum profile of ABT-594 and morphine, whereas celecoxib (COX-2 inhibitor) and gabapentin show specificity for activity in models of inflammatory and neuropathic pain respectively. In the mouse abdominal constriction assay (ACA) model, a putative model of visceral pain, all three compounds exhibit full efficacy, with A-366833 being particularly potent in this model relative to its potency across the various rat models (Figure 10).

Table 2. In Vivo Efficacy Profile of Most Promising Leads.

Compound	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)	Withing Pain (Mouse ACA)
ABT-594	+++ (0.08 $\mu\text{mol/kg}$ )	+++ (0.1 $\mu\text{mol/kg}$ )	+++ (0.03 $\mu\text{mol/kg}$ )	+++ (0.048 $\mu\text{mol/kg}$ )
A-312046	+++ (1.8 $\mu\text{mol/kg}$ )	+++ (0.7 $\mu\text{mol/kg}$ )	+++ (1.9 $\mu\text{mol/kg}$ )	+++ (0.3 $\mu\text{mol/kg}$ )
A-366833	+++ (3 $\mu\text{mol/kg}$ )	+++ (5 $\mu\text{mol/kg}$ )	++ (6 $\mu\text{mol/kg}$ )	+++ (0.11 $\mu\text{mol/kg}$ )
Celecoxib	++ (30 $\mu\text{mol/kg}$ )	+ (30 $\mu\text{mol/kg}$ ) <sup>*</sup>	0	N.T.
Morphine	+++ (3 $\mu\text{mol/kg}$ )	+++ (10 $\mu\text{mol/kg}$ )	++ (3 $\mu\text{mol/kg}$ )	+++ (1.3 $\mu\text{mol/kg}$ )
Gabapentin	+ (300 $\mu\text{mol/kg}$ ) <sup>*</sup>	++ (100 $\mu\text{mol/kg}$ )	0	N.T.

+++ is >75% efficacy; ++ is 40-75% efficacy; + is 20-40% efficacy; 0 is no activity.  
Values in parenthesis represent ED<sub>50</sub> values, all compounds administered i.p.  
<sup>\*</sup> Minimal dose producing a statistically significant change from saline control.  
N.T. = Not tested

Figure 8. Evaluation in Chung Model of Neuropathic Pain

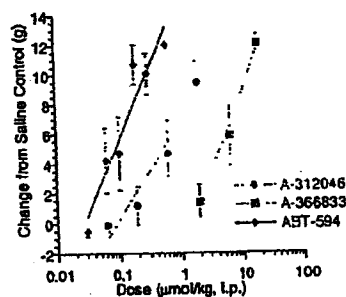


Figure 9. Evaluation in Formalin Model of Persistent Nociceptive Pain

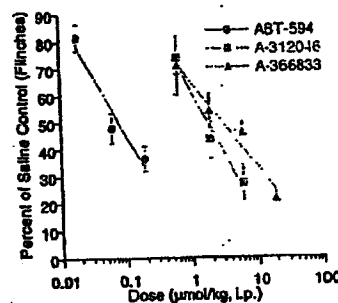
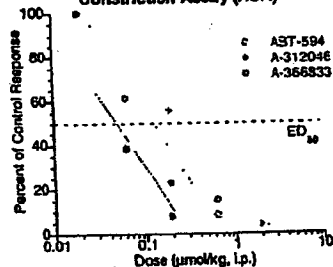


Figure 10. Mouse Abdominal Constriction Assay (ACA)

**GI Tolerability Profile:**

Nausea and emesis have been identified as significant adverse events clinically for ABT-594. The ferret emesis model has been used to quantify emesis in a preclinical model and evaluate the emetic potential of novel compounds. The no emesis threshold dose (highest dose to produce no emesis) for ABT-594, A-312046, and A-366833 was 0.01, 1.0, and 10  $\mu\text{mol/kg}$ , i.p., respectively. Thus, A-312046 and A-366833 exhibit approximately a 100-fold and 1000-fold shift in emetic liability relative to ABT-594.

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**CNS Side Effect and Safety Profile:**

Within the therapeutic range, ABT-594 produces an array of qualitative effects on rodent behavior, including prostration, labored breathing, ataxia, head weaving, loss of motor coordination and increased urination. Beyond the therapeutic range, additional effects include seizures and deaths. Qualitatively, both A-312046 and A-366833 exhibit a pronounced lessening, or even absence of many of these observable changes within their therapeutic ranges. Certain of these effects, including motor coordination and balance (rat edge test), seizure threshold (mice), and ALD (mice) can be readily quantified (Table 3).

**Table 3. Safety profile of Best Leads.**

Model	ABT-594 ( $\mu\text{mol/kg}$ , Lp)	A-312046 ( $\mu\text{mol/kg}$ , Lp)	A-366833 ( $\mu\text{mol/kg}$ , Lp)
Seizure Threshold (Mice, Approx $\text{ED}_{50}$ )	1.9	320	>400*
Approx. Lethal Dose (Mice, $\text{ED}_{50}$ )	19	300	>400*
Edge Test (Rats, $\text{ED}_{50}$ )	0.08	15	>19**

\* No deaths or seizures observed at highest dose (400  $\mu\text{mol/kg}$ ) tested.

\*\* Approx. 30% decrease in latency to fall at highest dose tested.

**Therapeutic Index Calculations:**

The ratio of effective dose in either the Chung model of neuropathic pain, the formalin model of persistent pain, or the mouse ACA model of visceral pain to the dose required to produce effects in various models of side effect liability can be used to calculate an approximate therapeutic index for ABT-594, A-312046, and A-366833 (Table 4). The values in boldface (Table 4) are where efficacy and side effect are measured in the same species by the same route of administration. A consistent pattern of improved therapeutic index is observed for both compounds independent of side effect model or efficacy model selected. Of particular importance to the clinically recognized dose-limiting side effect of emesis, A-312046 and A-366833 exhibit a 5- to 27-fold improvement in therapeutic index relative to ABT-594.

**Table 4. Therapeutic Index of Best Leads.**

Model	Ferret Emesis (No Effect Dose)	Rat Edge Test ( $\text{ED}_{50}$ )	Mouse Seizure Threshold ( $\text{ED}_{50}$ )	Mouse ALD ( $\text{ED}_{50}$ )
ABT-594 Chung ( $\text{ED}_{50}$ )	0.1	0.8	19	190
Formalin ( $\text{ED}_{50}$ )	0.12	1	24	240
Mouse ACA ( $\text{ED}_{50}$ )	0.21	1.7	40	400
A-312046 Chung ( $\text{ED}_{50}$ )	1.4	21	480	430
Formalin ( $\text{ED}_{50}$ )	0.58	10	215	200
Mouse ACA ( $\text{ED}_{50}$ )	3.3	50	1100	1000
A-366833 Chung ( $\text{ED}_{50}$ )	2	>12	>80	>80
Formalin ( $\text{ED}_{50}$ )	3.3	>18	>133	>133
Mouse ACA ( $\text{ED}_{50}$ )	90	>540	>3600	>3600

The clinical trial data with ABT-594 suggest that at least some level of efficacy is being observed at a dose (75  $\mu\text{g}$  bid) where emesis is minimal. Thus, the calculated T. I. from the preclinical models of 0.1 to 0.12 may represent a gross under-estimation of the tolerability of this compound. To better put into perspective the expected clinical therapeutic index of A-312046 and A-366833, the calculated improvements in therapeutic index (using the formalin and Chung efficacy models) relative to ABT-594 are presented in Table 5. Inclusion of data from the ACA model for A-312046 and A-366833 would yield T.I. improvements for emesis relative to ABT-594 of 16-fold and 430-fold respectively.

**Table 5. Relative Therapeutic Index Improvements vs. ABT-594 for Best Leads.**

Adverse Event	Therapeutic Index Improvement vs. ABT-594	
	A-312046	A-366833
Emesis (Ferret)	5 - 14x	20 - 27x
Seizure Threshold (Mouse)	4 - 11x	>11x
Edge Test (Rat)	10 - 24x	>15x

Analysis of therapeutic index based on peak plasma concentrations produces comparable values, with ABT-594 and A-312046 remaining relatively unchanged, and A-366833 producing a somewhat more favorable index (Table 6).

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Table 6. Therapeutic Index of Best Leads Based on Peak Plasma Concentrations.

	ABT-594	A-312046	A-366833
Peak Plasma concentration at ED <sub>50</sub> in Formalin Model (ng/ml)	2.6	43.7	108
Peak Plasma Concentration at Maximal Non-emetic Dose in Ferret (ng/ml)	0.46	26.5	1242
Therapeutic Index (Based on Peak Plasma Conc.)	0.17	0.61	11.5
Therapeutic Index (Based on Dose)	0.12	0.56	3.3

**Cardiovascular Safety Profile:**

A-312046 and A-366833 have undergone a preliminary evaluation in the canine Purkinje fiber repolarization assay. A-312046 produced no changes in action potential duration at 10 and 100-fold above therapeutic plasma concentration. A-366833 produced no significant effects at 10-fold above the therapeutic plasma concentration, but did produce an approximately 40% change in action potential at 100-fold above the therapeutic concentration. Both of these studies were performed in the absence of plasma. Correcting for plasma protein binding, the concentration intervals above therapeutic plasma concentration are approximately 20 and 200 fold.

A-366833 has undergone preliminary evaluation in the anesthetized dog preparation. A series of three thirty-minute infusions of A-366598 produced peak plasma concentrations of  $205 \pm 33$ ,  $851 \pm 124$ , and  $2512 \pm 646$  ng/ml (mean  $\pm$  SD) in the anesthetized dog. Preliminary analysis ( $n=4$ ) suggests plasma concentrations of A-366833 up to  $851 \pm 124$  ng/ml (8.5-fold therapeutic C<sub>max</sub>; rat formalin model, 12-fold above therapeutic plasma concentration at ED<sub>50</sub> in rat formalin model) exert no effect on QTc compared to vehicle treated controls. As plasma levels increased to  $2004 \pm 406$  and  $2512 \pm 646$  ng/ml, (20- to 25-fold of C<sub>max</sub>, 30 to 36-fold therapeutic at ED<sub>50</sub>) QTc increased  $23 \pm 10$  and  $30 \pm 8$  msec ( $n=4$ ; mean  $\pm$  sem) above pretreatment values, respectively, versus increases of  $14 \pm 3$  and  $16 \pm 3$  msec for vehicle controls ( $n=6$ ). Subsequently, at 30 and 60-minutes post infusion, QTc values were similar for drug and vehicle treated animals ( $944 \pm 167$  ng/ml). Although analysis of the full data set is incomplete, preliminary analysis suggests A-366833 produces a modest, dose-dependent increase in QTc. An unusually large difference in QTc interval between the saline control and drug groups at baseline (time = 0,  $\Delta$ QTc = 30 ms) was observed in this study. Plans are in place to add additional dogs to this study, and to complete the cardiovascular evaluation of A-312046.

The effects of A-366833 on other hemodynamic and cardiovascular parameters in the anesthetized dog were similar to those of ABT-594. In response to infusion of A-366833 mean arterial pressure was not affected by a plasma concentration of  $205 \pm 33$  ng/ml; mean arterial pressure decreased approximately 40 mmHg below baseline at the end of the second dose ( $851 \pm 124$  ng/ml), and remained at or near these levels during the high dose ( $2512 \pm 646$  ng/ml) and also during the 60-minute post-treatment period ( $944 \pm 167$  ng/ml). Heart rate and indices of cardiac contractile function increased modestly and transiently in response to A-366833; systemic vascular resistance decreased in a modest, dose-dependent manner. Pulmonary vascular resistance and cardiac output remained unchanged.

**Pharmacokinetics:**

The pharmacokinetic profile of A-312046 and A-366833 relative to ABT-594 in rat, dog, and monkey are outlined in Table 7. The poor oral bioavailability and high clearance rate of A-312046 and dog and monkey has prompted the evaluation of alternative routes of administration and/or prodrug approaches to the delivery of this compound. A-366833 exhibits excellent bioavailability across all three species. Metabolism studies are ongoing to enable prediction of human pharmacokinetic parameters.

Table 7. Pharmacokinetic Profile of Best Leads.

		t <sub>1/2</sub>	CL <sub>p</sub>	%F
ABT-594	Rat	1.5 h	1.7	61%
	Dog	4.7 h	0.4	35%
	Monkey	1.4 h	1.7	80%
A-312046	Rat	3.0 h	1.95	80%
	Dog	1.4 h	2.89	13%
	Monkey	1.5 h	2.36	3%
A-366833	Rat	1.5 h	3.02	73%
	Dog	2.6 h	0.35	109%
	Monkey	2.5 h	0.53	74%

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#### Compound-Related Issues:

A composition of matter patent application explicating claiming A-312046 was filed on Oct. 27, 1997 (by NeuroSearch), the U.S. application was filed on 10/27/98, and the World application published six months after that filing. The world application filing would be described as broed by Abbott standards. The Abbott-NeuroSearch research collaboration gives exclusive rights to the development of A-312046 to Abbott. A-366833 is described in an April 2000 U.S. filing, with a C.I.P. and world application to follow in April of this year. No publication has occurred nor have any office actions been received.

A-312046 is prepared in a single step from two readily available and inexpensive chemicals. Cost of goods have not been calculated but are expected to be inconsequential. A-366833 was originally prepared via a 21-step synthesis in enantiomerically pure form. Process research (D-45L) has begun process improvement within the last two months, and the synthesis currently stands at 16 steps.

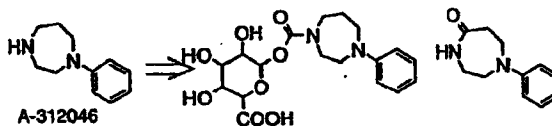
#### Medicinal Chemistry Advances

##### SAR Leading to A-312046:

Extensive SAR studies in the homopiperazine series have confirmed that substituents on the pyridine have powerful effects on subtype selectivity and *in vivo* activity. Small substituents at the pyridine 5-position that contain heteroatoms or  $\pi$ -systems often enhance selectivity for  $\alpha 4$ -containing subtypes. For example, hydroxyl, carboxamide, ethynyl, cyano, and azido groups all lead to improved selectivity at the  $\alpha 4\beta 2$  receptor vs. the  $\alpha 3\beta 4$  subtype. The selectivity is often at the expense of overall potency and efficacy, but activity at  $\alpha 3$ -containing receptors is attenuated to a greater extent than that at  $\alpha 4$  subtypes. The range of useful substituents is limited, because bulkier groups cause loss of agonist activity for all subtypes. Other limits pertain to *in vivo* potency. Polar substituents, such as the hydroxyl group, tend to partition to the CNS poorly and have in general failed to exhibit broad-spectrum analgesic efficiency. Conversely, incorporation of a halogen (Br or Cl) at the 6-position increases potency for both *in vitro* and *in vivo* assays, but with concomitant loss of subtype selectivity and increased side effect liability.

A-312046 was selected as an optimized candidate from a series for structurally related homopiperazine analogs based on *in vitro* separation between activity at the  $\alpha 4\beta 2$  and  $\alpha 3\beta 4$  receptor subtypes coupled with excellent efficacy across pain models and enhanced separation between efficacy and emetic liability relative to ABT-594. A-312046 exhibited excellent oral bioavailability and long half life in the rat ( $F=80\%$ ,  $t_{1/2}=3$  h), but failed to provide acceptable oral bioavailability in either the dog or monkey (13% and 3% oral bioavailability respectively). GI absorption studies in the dog using radiolabelled A-312046 demonstrated >95% absorption, and subsequent studies (both *in vivo* and *in vitro*) implicated rapid first-pass metabolism. Two major metabolites were identified, both involving metabolism of the basic nitrogen (Figure 11). Consequently, it was reasoned that delivery of A-312046 to the general circulation, bypassing the gut may be a viable approach to improving the pharmacokinetic shortcomings of this molecule. Two alternate strategies for delivery of 312046 are currently being assessed. The first involves evaluation of a transdermal (patch) dosing of A-312046. The physical properties of this compound (low MW, highly soluble, nicotine-like) are conducive to transdermal delivery. A theoretical estimate for the permeability of A-312046 through human skin has been established (D4P7), which predicts that it will be feasible to deliver up to 30 mg/day. Based on extrapolation of clinical doses of ABT-594, an efficacious dose of A-312046 is likely to be well within this amount. Moreover, a patch formulation may have advantages over oral administration in that local effects in the gut that may contribute to emesis are avoided, and transdermal delivery may allow more sustained plasma levels while blunting the rise to  $C_{max}$ .

Figure 11. Metabolism of A-312046



The second strategy would deliver A-312046 via a prodrug derivative that can be administered orally. For oral administration, the prodrug should be well absorbed and protected from the first-pass metabolism that depletes A-312046. The primary site of metabolism for A-312046 (oxidation, glucuronidation) is the basic nitrogen on the homopiperazine. Carbonyl derivatives at this site are not subject to these processes. For example, the *p*-aminophenyl carbamate of A-312046 (A-345151) is well-absorbed following oral administration in dog, and achieves high plasma levels. Unfortunately, the compound converts very slowly to A-312046 in plasma, precluding accumulation of therapeutic levels of the active compound. To date, more than 70 potential prodrugs of A-312046 have been screened (D4EK) for their ability to convert to A-312046 during 2h incubation in dog or human plasma. Simple amides and carbamates do not convert to A-312046 under these conditions. On the other hand, a set of carbamates designed for 'cascade' cleavage with a remote ester or anilide trigger, effectively deliver A-312046 in plasma. For

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one of these, A-367032, oral administration in dog provides plasma levels of A-312046 nearly twice as high as direct dosing of the parent, but only very small amounts of the prodrug are detected. The pharmacokinetic profile suggests effective delivery of A-312046 over the first two hours until prodrug is depleted, at which time the circulating levels of A-312046 begin to drop rapidly. The acetate trigger may be too sensitive, and it appears that the prodrug is substantially hydrolyzed in the time frame required for absorption. More sterically encumbered esters have now been prepared (See Figure 14), and are currently being evaluated in vivo.

Figure 12. Pharmacokinetic Profile of A-345151

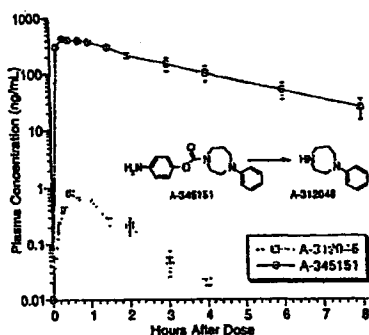


Figure 13. Pharmacokinetic Profile of A-367032

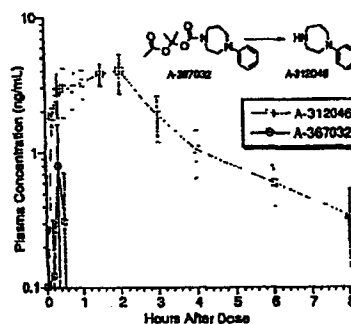
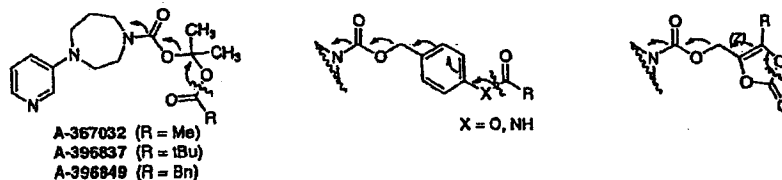


Figure 14. Cascade Prodrugs of A-312046



#### SAR Leading to A-366833

The SAR of the fused azetidine series exemplified by A-366833 is just beginning to emerge, and great sensitivity to structural changes is already evident. A-366833 is a partial agonist of modest potency at  $\alpha_4$  subtypes, but shows very little activity at the ganglionic ( $\alpha_3$ -containing) subtypes. In sharp contrast, the enantiomer A-365193 exhibits comparable partial efficacy and potency at both the ganglionic receptor and  $\alpha_4\beta_2$  subtype. This trend holds for some, but not all members of the series – the 6-Cl pyridine analogs are full agonists at all subtypes, with nearly indistinguishable profiles.

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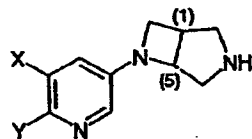
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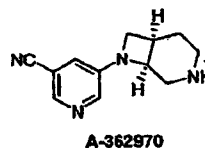
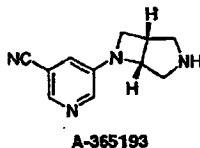
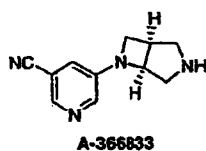
Table 8. SAR of 3,6-Diazabicyclo[3.2.0] Core.



A-Number	X	Y	Ring Stereochemistry	$\alpha 4\beta 2$ (EC <sub>50</sub> , %Max)	$\alpha 3\beta 4$ (EC <sub>50</sub> , % Max)
A-366833	CN	H	1R, 5S	4.6 $\mu$ M, 63%	16%
A-365193	CN	H	1S, 5R	9.3 $\mu$ M, 32%	19 $\mu$ M, 37%
A-366956	CN	Br	1R, 5S	0.32 $\mu$ M, 100%	2.1 $\mu$ M, 105%
A-361731	H	H	1R, 5S	2.2 $\mu$ M, 82%	30 $\mu$ M, 67%
A-361734	H	H	1S, 5R	2.3 $\mu$ M, 101%	32 $\mu$ M, 38%
A-361732	Br	H	1R, 5S	4.5 $\mu$ M, 33%	IA
A-365194	Br	H	1S, 5R	12 $\mu$ M, 16%	6.0 $\mu$ M, 29%
A-362124	H	Cl	1R, 5S	0.54 $\mu$ M, 133%	5.5 $\mu$ M, 145%
A-361733	H	Cl	1S, 5R	0.35 $\mu$ M, 118%	7.6 $\mu$ M, 83%
A-365191	Acetylenyl	H	1S, 5R	12 $\mu$ M, 39%	41 $\mu$ M, 27%
A-365192	Vinyl	H	1S, 5R	IA	IA

Placement of the pyridine on the other nitrogen of the bicyclic diamine leads to substantially more potent, but essentially non-selective compounds. So far, these have shown only weak activity in animal pain models. Expansion of the four-membered ring results in a sharp loss of potency, but the other ring accommodates this change - A-362970 has a very similar in vitro profile to A-366833. Scale up is currently in progress for in vivo evaluation.

Figure 15. Alternative Core Structures.

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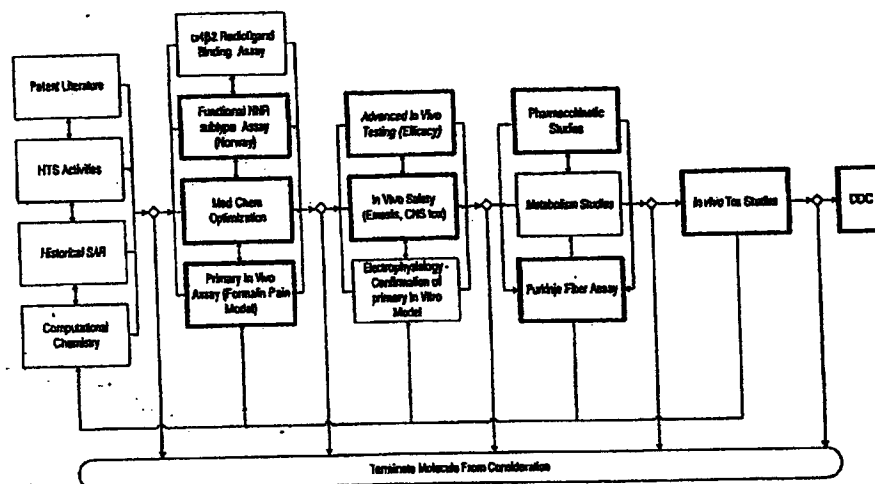
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Stage 1 • Lead Discovery • Lead Identification	Stage 2 • Lead Validation • Lead Optimization	Stage 3 • Lead Optimization	Stage 4 • Lead Optimization • Candidate Selection	Stage 5 • Candidate Selection
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The current critical path activities are highlighted in heavy red lines, the lighter black lines indicate assay systems that are valuable in understanding overall compound profile, but are not normally criteria for dropping a compound from consideration. The majority (70%) of the NNR project activity currently focuses on medicinal chemistry optimization and in vivo screening. The critical path in vitro screening is conducted, in large part, by our NeuroSearch collaborators in Norway. The remaining effort (30%) is focused on in vitro method development and screening that are predominantly of relevance to the identification of NNR-subtype selective compounds for indications outside of analgesia.

**Biology and Pharmacology**

- Potency.** All compounds are initially evaluated for potency, as measured by the binding of [<sup>3</sup>H]-cytisine to β2-containing NNRs (predominantly α4β2) in a rat brain homogenate. Throughput for complete concentration curves to generate K<sub>i</sub> values is 24 compounds per week.
- Subtype Selectivity.** The functional activity of potent compounds (K<sub>i</sub> < 100 nM) at the α4β2, α4β4, α3β4, and α3β2 NNR subtypes, as well as their agonist or antagonist properties, is determined through FLIPR methodology using recombinant human cell lines stably expressing these subtypes and the IMR 32 human cell line expressing native receptors, predominantly α3β4. Throughput for complete dose response curves is approximately 12 compounds (n=4) per week.
- Functional Activity. Behavioral Responses in Pain Models.** Several *in vivo* pain models are currently in use. These include rodent models that measure effects of compounds on acute, persistent, and neuropathic pain.
  - Acute Pain.** Rodent models for effects on acute pain include the mouse temperature, activity, analgesia (TAA) model (the TAA model assesses analgesic effects by hot plate methodology, as well as effects on temperature and activity), and the Hargreaves rat hot box model, both of which are currently used on a limited basis, when required for additional characterization of compounds. Throughput in these models is generally one compound (3 doses each) per week.
  - Persistent Pain.** Effects on persistent chemical pain are assessed using the rat formalin model. This model is used as the primary screen. Throughput in the formalin model is 3-4 compounds (3 doses each) per week.

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- c. Neuropathic Pain. Effects on neuropathic pain are assessed using the rat Chung model. Only selected compounds are evaluated in this model since it is highly labor intensive. This model requires ligation of the 5<sup>th</sup> and 6<sup>th</sup> lumbar nerves. After a two-week recovery period, a ½ day session is then required to obtain a full dose response for a single compound. Throughput is 3 compounds per week.
- d. Additional Behavioral Models. Several additional pain models are in place, including the mouse abdominal constriction assay for visceral pain; throughput in this assay, when required is one compound (three doses) per week.
4. Emetic, cardiovascular and other side effects. Emetic effects are evaluated in ferrets within the Project and also in collaboration with Integrative Pharmacology. Throughput in the ferret emesis model within the Project is 3 compounds (single dose) per week. For compounds of interest a complete dose response curve is generated. Selection of the dose for ferret emesis studies is initially based on the potency observed in i.p. dosing in the rat formalin model of persistent pain. Cardiovascular effects are evaluated in dogs, which appear to be the most sensitive species for NNR-mediated changes in blood pressure and heart rate. For compounds of particular interest, seizure threshold is assayed in mouse. Additionally, an attempt to measure dizziness is assayed using an edge test in rats and a rotarod test in mice. Throughput for these assays is generally one compound per week, when required.
5. Functional Activity: Neurotransmitter Release. Evaluation of the effect on neurotransmitter release provides a biochemical link between the direct effect of the compound on the NNR as measured in functional assays and the behavioral response in the *in vivo* pain models. *In vitro* neurotransmitter release assays are in place that measure the release of dopamine from either rat striatum or cortex, and the release of norepinephrine from either hippocampus or thalamus. For screening purposes, dopamine release in striatum and norepinephrine release in hippocampus are measured. Throughput for a 7 point dose response curve is 4 compounds (n=3) per week for each neurotransmitter. *In vitro* assays are also being developed to measure serotonin or GABA release from rat or mouse brain. In addition, procedures are in place for *in vivo* microdialysis of striatum, thalamus, hippocampus and spinal cord to measure the effects of compounds on the *in vivo* release of dopamine, norepinephrine, and serotonin.
6. Pharmacokinetics. In addition to characterization of potential lead compounds, pharmacokinetic analysis of representative subtype-selective compounds is necessary to enable proper interpretation of *in vivo* results from efficacy and side effect models. Typical studies on compounds of interest include detailed pharmacokinetic measurement of plasma concentrations of compound after i.v. or oral dosing, and also pharmacokinetic measurement of brain and plasma concentrations of compound after i.p. dosing in the rat. Throughput is one compound/week.

Electrophysiological assay. The Parallel Oocyte Electrophysiology Tester system (POETs), a throughput-enhanced electrophysiology instrumentation, has recently been developed and validated within the Project in collaboration with Automation Engineering. With the present system of six oocytes in parallel a significantly enhanced throughput over standard electrophysiological methodology, with assay of over 100 compounds per day (single concentration assayed in duplicate) is possible.

#### Medicinal Chemistry

Current work is directed toward expansion of the SAR around 366833. Planned analogs of 366833 have been chosen to provide the best chance for *in vivo* activity with overall selectivity. Pyridine substitutions include 5- ethynyl, cyano, methoxy, halo, azido, carboxamide, and methyl, with and without a 6-halogen in place. Reasonable quantities of both enantiomeric diamine cores are available to prepare this limited series. Likewise, the same derivatives are targeted for the homologous 3,8-diazabicyclo[4.2.0]octane series. Finally, N-alkyl derivatives of some of the very potent (and non-selective) 3-pyridinyl-3,8-diazabicyclo[3.2.0]heptanes will be evaluated. For the diamine series, like the pyridinyl ethers, N-alkylation causes a sharp attenuation in agonist activity that is more dramatic at the  $\alpha 3$  subtypes. The exceptional potency of the NH analogs suggests that N-alkyl versions may retain sufficient  $\alpha 4$  activity to be effective analgesics.

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Figure 16. SAR Plans for Diazabicyclo Core Structure.



## Competition

### Within Project Approach

Company	Compound	Indication	Status of compound	Status of project
<b>Nicotinics:</b>				
Eisai/Cyto-Med	(±)-Epibatidine analogs	Pain	Preclinical	Active
Taiho	GTS-21	Alzheimer's	Phase II	Seeking development partner
SIBIA Neuroscience (Rights to Lilly)	SIB-1508Y	Parkinson's Disease	Phase II	Discontinued
SIBIA Neuroscience (Rights to Lilly)	SIB-1553A	Alzheimer's	Phase II	Discontinued
SIBIA Neuroscience (Merck)	SIB-T1887	Pain	Preclinical	Unknown
Aventis/Targacept	RJR-2403	Alzheimer's	Phase I	Discontinued (PK issues)
Pharmacia	Unknown	Multiple	Preclinical	Active - focusing on α7
Pfizer	Cytisine analogs	Alzheimer's, pain	Phase I, compound unknown	Active
Astra Zeneca	AR-17779	Cognition, pain	Preclinical	Active - patent application on α7 selective compounds
Eli Lilly	Unknown	Multiple	Preclinical	Obtained exclusive license to human NNRs from SIBIA prior to acquisition of SIBIA by Merck
NeuroSearch	Multiple series	Pain, depression	Preclinical	Exclusive compound license to Abbott
NeuroSearch	NS-3573, 3956, 3939, 3890	Smoking cessation	Preclinical	Seeking licensing partner
Johnson and Johnson	Pyridyl ethers	Pain, Alzheimer's	Preclinical	Patent activity (NeuroSearch holds clear priority over published J&J patent)
Novo Nordisk		Alzheimer's	Preclinical	Patent activity
Univ. of Milan	DBO-83	Pain, Cognition	Preclinical	Collaboration with Abbott
<b>Muscarinics:</b>				
Lilly	LY-297802	Pain	Phase II (Discontinued)	Continued patent activity
Merck	L-689660	Alzheimer's, Pain	Preclinical	Unknown
Sandoz-Synthelabo	Pyridinyl diamines	Pain	Preclinical	Patent Activity

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Neurological and Urological Diseases Research  
1001

Discovery Project Review  
NNPs – ABT-594 Backup  
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Within Therapeutic Area – Focus on Neuropathic Pain

Product	Company	US Development Phase	Class/MOA	Comments
Pregabalin	Parke-Davis	III	Ca channel $\alpha 2\delta$ ?	Also for epilepsy, chronic pain – may be tox. issues affecting ongoing clinical trials
GV 196711	Glaxo	II	Glycine antagonist	Neuropathic pain and chronic pain
Memantine	Merz	II	NMDA antagonist	Dose ranging trial with 375 patients now underway
PN 401	ProNeuron	II	Unknown	For disease modification of PDN – pain and numbness next
Prosaptide	Myelos	II	Unknown	14 amino acid peptide Pain associated with nerve injury
Resiniferatoxin	Afferon	II	Vanilloid	Topical capsaicin analog
LTA	Astra	II	Sodium channel blocker	Topical w/ longer duration of action than capsaicin
CNS 5161	Cambridge Neuroscience	II	NMDA antagonist	Will not move to Ph II until a development partner is found

Competitive Analysis

Prescription analgesics to treat pain can be grouped into four classes; opioids, NSAIDs, other non-opioids and adjuvants. Opioids and combination agents are generally used to treat acute pain and cancer pain of moderate to severe intensity, but have AE and dependence liabilities. NSAIDs (including COX-2 inhibitors), have very good tolerability, but have only moderate efficacy and anti-inflammatory activity, and are used to treat pain of mild to moderate intensity. Tramadol is sometimes substituted for NSAIDs to treat chronic pain or pain of moderate intensity, but has much higher AE's than the NSAID class. Adjuvant analgesics are drugs such as tricyclic antidepressants and antiepileptic drugs have efficacy in the treatment of neuropathic pain, but offer only partial pain relief, have low (50%) responder rates, and undesirable AEs.

Pipeline compound Pregabalin, an anticonvulsant with MOA thought to be similar to conventional AEDs, may reach market well before the NNR compound. Recently identified toxicological issues from preclinical mouse studies have put the future of this compounds somewhat in doubt. Pregabalin is similar to Neurontin, but is more potent, has a wider therapeutic index and longer half-life, with potential for better efficacy and/or better side-effect profile than Neurontin. Generic Neurontin will also be available. However, unmet need is expected to remain high in neuropathic pain, since pregabalin will likely achieve only partial pain relief and low responder rates, as is found for other AEDs used in the treatment of neuropathic pain.

An NNR achieving the target profile outlined above would represent a breakthrough in treatment of moderate to severe pain, offering pain relief superior to NSAIDs without the AE liabilities of the opioids. The novel MOA of the NNR also offers potential for significantly improved pain relief and/or responder rates for neuropathic pain vs. gold standards. Numerous other companies are exploring NNR compounds and other MOAs that could also achieve the target profile. Entering the market after the competition, with a similar profile, would impact the commercial opportunity; however, the large market size, inter-patient variability regarding efficacy and tolerability of various agents, significant use of combination therapy, and high level of switching would likely make later entries viable, particularly if MOA remains a differentiating feature.

Competition within the NNR field is expanding rapidly. With the acquisition of SIBIA Neuroscience, Merck has become an important competitor. Lilly currently holds license to the SIBIA DNA patents, but rights are to revert to Merck at the end of this current licensing agreement. Pharmacia has had an active program for the past three years. Astra Zeneca, Pfizer, Targacept, and Johnson and Johnson all appear to remain active in this area.

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Neurological and Urological Diseases Research  
1Q01Discovery Project Review  
NNRs - ABT-594 Backup  
20**Project Team**

Individual	Expertise	Activities	% time
Carol Surowy	Bio GL	Coordination of in vitro and in vivo biology program	100
Clark Briggs	Electrophysiology	Identification of high affinity $\alpha 4\beta 2$ subform selective compounds; planning and setup of $\alpha 7$ program for schizophrenia	100
Dave McKenna	Electrophysiology	POETs screening, assay methods development	100
Pamela Pultarcken	Pharmacology	Neurotransmitter release assays, methods development	100
Iris Jacobs	Pharmacology	Neurotransmitter release assays	100
Dave Anderson	Pharmacology	Radioligand binding assays, data analysis	100
Jerry Budzik	Pharmacology	5-HT <sub>2</sub> assay, risoxetine binding assay development	100
Jeff Campbell	Pharmacology	In vitro functional screening, ferret emesis model	100
Rama Thimmapaya	Mol. Biology	Cloning and expression of ferret NNR subtypes, stable cell line development	100
Brent Putman	Mol. Biology	Cloning and expression of ferret NNR subtypes, stable cell line development	100
Lynne Rueter	Behavior	Chung neuropathic pain model, mechanistic studies, development of anxiety and depression models	100
Kathy Kohlhaas	Behavior	Chung model, anxiety models	100
Pete Curzon	Behavior	Various pain models, development of schizophrenia models	100
Mike Buckley	Behavior	Pain models, antidepressant screening	100
Bill Bunnelle	Chem. GL	Coordination of chemistry program, patent preparation	100
Mick Dart	Med. Chem.	Prodrugs of A-312046	100
Anwer Basha	Med. Chem.	Prodrugs of A-312046	100
Mike Schrimpf	Med. Chem.	A-366833 analogs, $\alpha 4$ -selective compounds	100
Jianqiao Ji	Med. Chem.	A-366833 analogs	100
Jennifer Pace	Med. Chem.	Ring expanded 833 analogs, bridged analogs	100
Kevin Sippy	Med. Chem.	A-366833 analogs, $\alpha 4$ -selective compounds	100
Karin Tietje	Med. Chem.	Ring expanded analogs, bridged analogs	100
Keith Ryther	Med. Chem.	Prodrugs of A-312046	100

**Technology and Support Groups**

Group	Current FTEs	Priority (1-3)*	Milestone Date†	Description of Outcome Desired by Milestone Date
HTS Screening	0	2	9/01	Radioligand binding HTS against $\alpha 7$ receptor.
Automation Engineering	1	1	03/01	Development of HTS POETs, behavioral screening automation
Process Chemistry	4.5	1	3/01	Development of improved synthetic route to A-366833 and delivery of sufficient material for 2-week toxicology study in rats
PK and Metabolism	1	1	5/01	Evaluation of prodrug analogs of A-312046. Comparative assessment of metabolism profiles of ABT-594, A-312046, and A-366833. Evaluation of additional new lead structures
Toxicology	0	1	5/01	Two-week rat tox. studies on A-312046 and A-366833
Integrative Pharmacology	0.2	1	4/01	Cardiovascular evaluation of A-312046 and A-366833. Purkinje fiber assay of compounds related to A-312046 and A-366833 to evaluate SAR
Formulation	0.2	1	5/01	Solubility and stability assessment of A-312046 and A-366833

Total FTEs

6.9

\* Priority: 1 = Must have, 2 = Should have, 3 = Nice to have  
† Avoid "ongoing". Provide specific dates to achieve milestone.HIGHLY  
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#### External Resources

Organization	Activities
NeuroSearch: In vivo pharm.	5.6 Headcount: Cloning and expression of human NNR subtypes, development of stable cell lines, FLIPR screening of collaboration compounds, $\alpha 7$ radioligand binding assay
NeuroSearch: In vivo	2.7 Headcount: Evaluation of collaboration compounds in models of depression and anxiety.
NeuroSearch: Chemistry	2.7 Headcount: Synthesis of compounds for pain, depression and schizophrenia targets.

#### Adequacy and Optimization of Resources

Resources are adequate at this time for the identification of a follow-on to ABT-594 by 2Q/01. The project team is on track for establishing the identification of NNR modulators of the  $\alpha 7$  subtype as the next molecular target. The therapeutic indications for  $\alpha 7$  are most likely to include schizophrenia, and in particular the cognitive deficit aspects of schizophrenia.

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## **Meyer Deposition Exhibit 18**

**P's Exhibit FD**

Elizabeth  
Kowaluk/LAKE/PPRD/A.  
BBOTT  
03/08/2001 05:19 PM

Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT,  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Bruce  
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K  
Biamesen/LAKE/PPRD/ABBOTT@ABBOTT, James  
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael D  
Meyer/LAKE/PPRD/ABBOTT@ABBOTT, James  
Steck/LAKE/PPRD/ABBOTT@ABBOTT, David C  
Ross/LAKE/PPRD/ABBOTT@ABBOTT, Nigel  
To Livesey/LAKE/AI/ABBOTT@ABBOTT, Laura  
Robinson/LAKE/AI/ABBOTT@ABBOTT, Howard S  
Cheskin/LAKE/PPRD/ABBOTT@ABBOTT, Walid  
Awni/LAKE/PPRD/ABBOTT@ABBOTT, David D  
Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W  
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Connie  
Faltynek/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep  
Dutta/LAKE/PPRD/ABBOTT@ABBOTT, Rosemarie K  
Waleska/LAKE/PPD/ABBOTT@ABBOTT  
John N Simons/LAKE/PPRD/ABBOTT@ABBOTT, Tim  
cc Vanbiesen/LAKE/PPRD/ABBOTT@ABBOTT, Steve C  
Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject ABT-594/Pain Strategy DSG - 3/5 Meeting Minutes

Thanks to all who attended last Monday's (3/5/01) meeting of the ABT-594/Pain DSG core team.

The meeting focused on summarizing key issues of concern for ABT-594, as a first step to framing and structuring the decision problem. The issues raised are summarized in the attached document. Please let me know if there is anything I have failed to capture, or if you have additional thoughts.

A number of issues were raised that apply more broadly to the subject of therapeutic area strategy, as well as specifically to ABT-594. These are collected at the end of the document in anticipation of future discussions - please note that this is not intended to be a comprehensive summary of issues related to pain strategy at this point.

At next week's meeting (Tuesday 3/13/01), we will review and discuss issues related to the NNR backups. As a starting point I will summarize those issues I have already become aware of through one-on-one discussions and background reading. I would also like to review a proposed approach to the development of a Pain Strategy at this meeting.



I look forward to seeing you next week. In the ABT-594-Pain DSG Core Team Minutes 3\_5\_01 meantime feel free to call (x84402) or e-mail with any comments or questions.

Liz

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ABBT298379

# **Meyer Deposition Exhibit 19**

**P's Exhibit FF**

**Calendar Entry**

☐ Appointment 
 ☒ Invitation 
 ☐ Event 
 ☐ Reminder 
 ☐ Anniversary

## Brief description:

Paul Andrews, PhD: ABT-594 Guest Speaker and Discussion  
 Location: Urology Work Room, AP30-3 SW Corner

Date:

03/12/2001

Time:

08:30 AM - 01:00 PM

☐ Pencil in☐ Not for public viewing

## Detailed description:

Paul Andrews, PhD  
 Department of Physiology  
 St. George's Hospital Medical School  
 London, UK

Paul Andrews, PhD, will be joining us for a discussion of ABT-594's tolerability issues, especially the emetic liability.

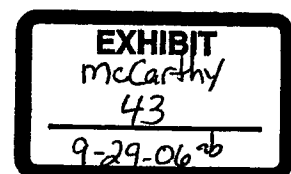
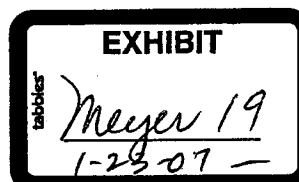
Please attend the discussion from 8:30 a.m. - 11:30 a.m. and join us for lunch from 11:30 a.m. - 12:30 p.m.

Bruce McCarthy  
 Marleen Verlinden

Invitations have been sent to: Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael D Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT, Mark A Osinski/LAKE/PPRD/ABBOTT@ABBOTT, Bryan F Cox/LAKE/PPRD/ABBOTT@ABBOTT, Richard G Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep Dutta/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Michael K Blanesen/LAKE/PPRD/ABBOTT@ABBOTT, Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT  
 Optional invitees: Amy M Wood/LAKE/PPRD/ABBOTT@ABBOTT, Amanda J Meier/LAKE/PPRD/ABBOTT@ABBOTT, Hope R Ceaser/LAKE/PPRD/ABBOTT@ABBOTT, Mary A Metz/LAKE/PPRD/ABBOTT@ABBOTT, Nancy M Palbicke/LAKE/PPRD/ABBOTT@ABBOTT, Ericka B Moore/LAKE/PPRD/ABBOTT@ABBOTT  
 Chairperson: Catherine K Kacos/LAKE/PPRD/ABBOTT

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ABBT 0022006



**Paul Andrews, PhD  
St. George's Hospital Medical School  
London, UK**

**Meeting Agenda  
Monday, 12 March 2001**

ABT-594 Discussion

Attendees: Marleen Verlinden, James Sullivan, Michael Meyer, Kennan Marsh, Walid Awni, Mark Osinski, Bryan Cox, Rick Granneman, Sandeep Dutta, David Morris, James Thomas, Michael Biarnesen, Aldona Matalonis, Bruce McCarthy

8:30 am – 9:45 am	ABT-594 Review: Preclinical Data Clinical Data	Mike Meyer Bruce McCarthy
9:45 am – 10:00 am	Break	
10:00 am – 11:00 am	Paul Andrews' Presentation Mechanisms of ABT-594 Induced Emesis	Paul Andrews
11:00 am – 12:00 pm	Discussion: Mechanism Hypothesis Generation Experiments Proposed Next Steps	
12:00 pm – 1:00 pm	Lunch	

Dexmedetomidine Discussion

Attendees: Marleen Verlinden, James Sullivan, Kennan Marsh, Bryan Cox, Mila Etropolski, Charles McLeskey, Michael Karol, Steven Buckner, Steve Collins, Victor Jorden, Bruce McCarthy

1:00 pm – 2:00 pm	Dexmedetomidine Review: Preclinical Data Clinical Data	Jim Sullivan Mila Etropolski
2:00 pm – 2:15 pm	Break	
2:15 pm – 4:00 pm	Discussion: Separation of Analgesics and CNS Effects	

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ABBT 0022007

	Dose (nmol/kg)	Retches & Vomits (avg # episodes)	Latency, min (vomitters only)	Vomiting incidence	%
ABT-594	30	—	—	0/3	0
(assayed	100	1	9.2	2/9	22
Jul-Sep '98)	300	2.7 ± 0.7	9.0 ± 2.2	5/9	56
	1000	5.7 ± 0.9	2.7 ± 0.4	3/3	100
ABT-594	10	1	12.5	1/6	17
(assayed Jul '00)	30	8	7	2/6	33
	100	10.7 ± 2.3	4.1 ± 0.4	6/6	100

Osinski/Seifert D46R  
09-Mar-01

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ABBT 0022008



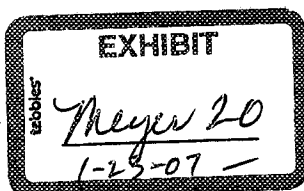


# **Meyer Deposition Exhibit 20**

## **D's Exhibit 792**

M99-114 Study Review

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ABBT 0001749

# M99-114 Neuropathic Pain

## *Study Results*

- Summary
- Study design
- Efficacy results
- Adverse events
- Conclusions and next steps

4/23/01 PRELIMINARY DATA

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ABBT 0001750

# M99-114 Neuropathic Pain

## Summary

- Efficacy
  - 150, 225 and 300 mcg BID are significantly better than placebo
  - All three doses may have similar efficacy
- Safety
  - 150 mcg BID
    - Nausea: 34%
    - Vomiting: 15%
    - Dizziness: 17%
    - Abnormal Dreams: 22%
  - Dose dependent increase in adverse events
- Conclusion
  - ABT-594 significantly reduces diabetic neuropathic pain

4/23/01 PRELIMINARY DATA

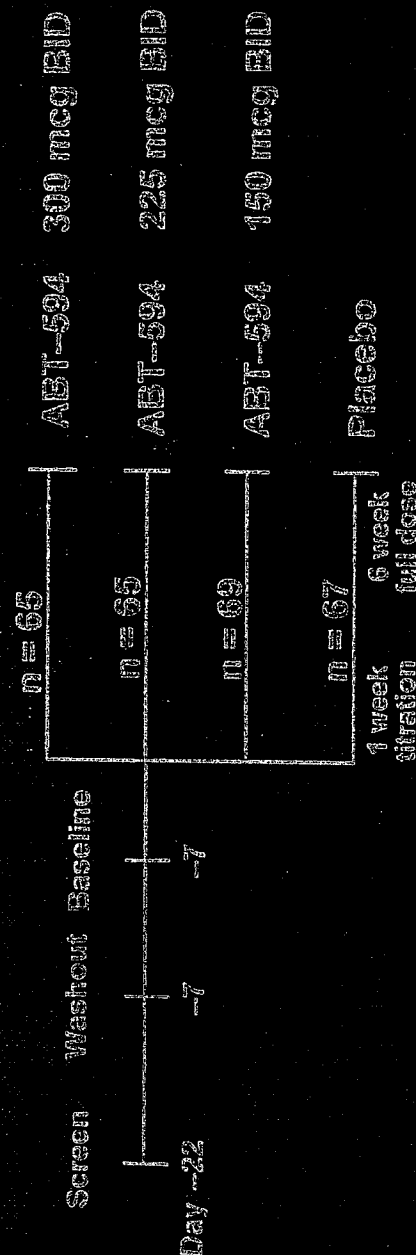
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ABBT 0001754

# M99-114: Neuropathic Pain

## Design

- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-day titration phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I PRELIMINARY
- Concomitant analgesics disallowed

4/23/01 PRELIMINARY DATA

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ABBT 0001762

## M99-114: Neuropathic Pain

### *Outcome Measures*

- Primary

- Weekly average of daily Pain Rating Scale (11-point Likert in a diary)
  - Change from baseline to last 7 days on drug

- Secondary

- Site-based Pain Rating Scale (11-point Likert)
- Neuropathic Pain Scale
- Patient Global Impression of Change
- Clinician Global Impression of Change
- SF-36

4/23/01 PRELIMINARY DATA

# M99-114: Neuropathic Pain

## Outcome Measures

### • Pain Rating Scale

0	1	2	3	4	5	6	7	8	9	10
no pain								worst pain possible		

### • Neuropathic Pain Scale (NPS)

- 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10
-----------	---	---	---	---	---	---	---	---	---	----

The most sharp  
sensation  
imaginable (like a  
knife")

### • Subject, Clinician Impression of Change

1	Much Improved
2	Moderately Improved
3	Minimally Improved
4	No Change
5	Minimally Worse
6	Moderately Worse
7	Much Worse

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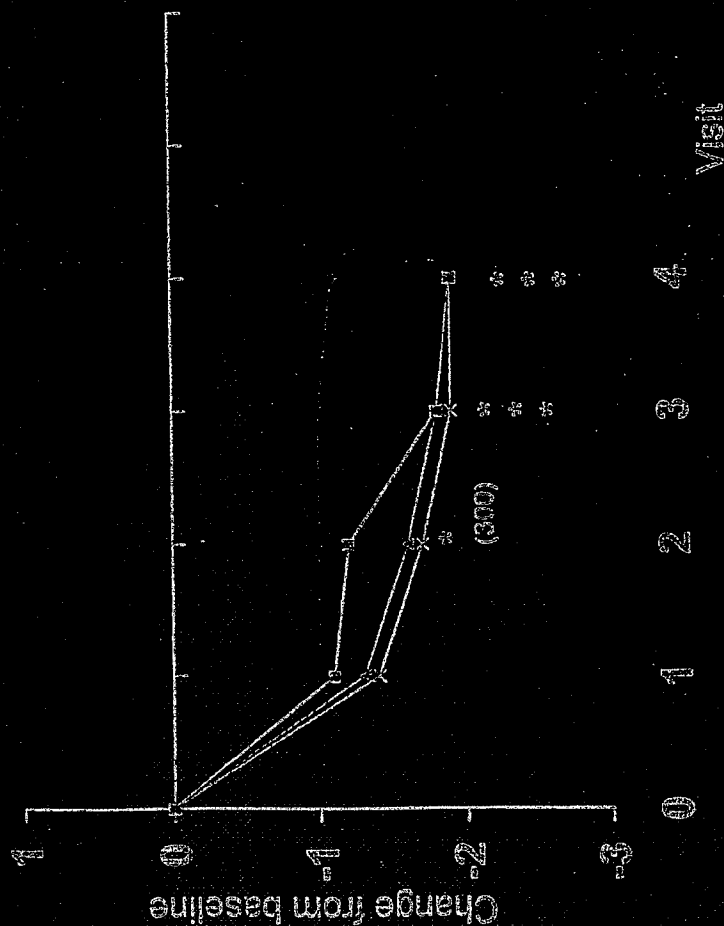
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# ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Primary Efficacy Variable in the Intent to Treat Population

*Pain Rating Scale-Diary (Between Visit Average) Change: to Baseline*

	Final
Placebo	↓ 17% *
—□— ABT-594 150 mcg BID	↓ 29% *
—▲— ABT-594 225 mcg BID	↓ 23% *
—*— ABT-594 300 mcg BID	↓ 30% *



Percent of subjects at visit 4  
 Placebo 87%  
 ABT-594 150 mcg BID 74%  
 ABT-594 225 mcg BID 58%  
 ABT-594 300 mcg BID 43%

\*p<0.05

Maximum possible decrease for 150 mcg BID group was 6.6

4/23/01 PRELIMINARY DATA

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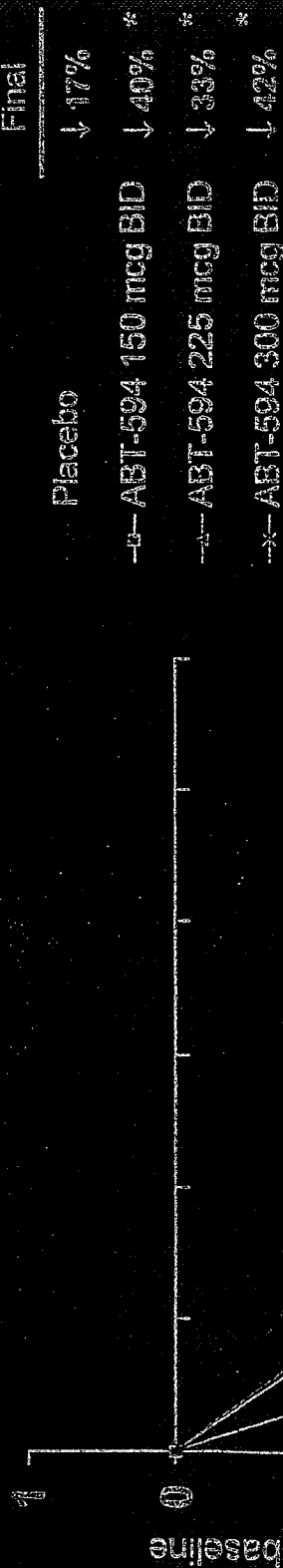
ABBT 0001766



# ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale in the Intent to Treat Population

Change:  
Baseline  
to  
Final

## Pain Rating Scale (Site Based)



\*p<0.05

Maximum possible decrease for 150 mcg BID group was 6.7

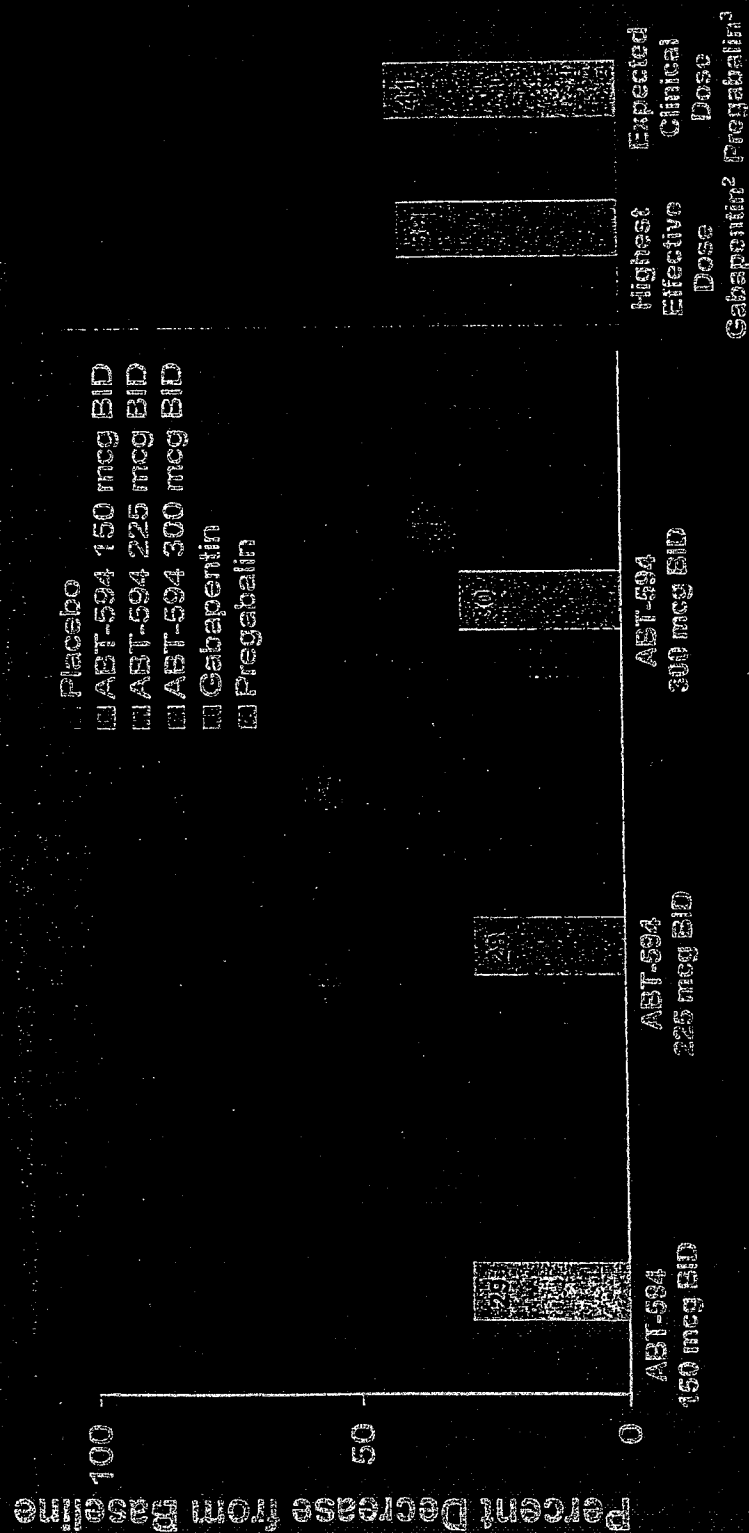
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ABBV 0001756

# ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain as Greatly as Gabapentin or Pregabalin (ITT)

## ABT-594 vs. Gabapentin and Pregabalin



1 11-point Likert scale week 7 vs. baseline  
 2 11-point Likert scale week 8 vs. baseline  
 3 11-point Likert scale week 5 vs. baseline

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ABBT 0001757

**ABT-594 150, 225 and 300 mcg BID Were Associated  
with a Dose Dependent Increase in Adverse Events,  
Especially Nausea, Vomiting and Dizziness**

*Adverse Events\**

Event	ABT-594		ABT-594	
	Placebo N = 65	150 mcg BID N = 65	225 mcg BID N = 69	300 mcg BID N = 67
Nausea	11 %	34 %	43 %	46 %
Abnormal Dreams	0 %	22 %	22 %	18 %
Headache	12 %	20 %	14 %	19 %
Dizziness	5 %	17 %	35 %	28 %
Vomiting	3 %	15 %	25 %	21 %
Diarrhea	3 %	11 %	12 %	6 %
Dyspepsia	3 %	8 %	12 %	7 %
Asthenia	2 %	6 %	16 %	19 %

\*Occurring in ≥5% 150 mcg BID ABT-594 treated patients and ABT-594 incidence > placebo.

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ABBT 0001758

# Meyer Deposition Exhibit 23

## D's Exhibit 661 – Part 1

# ABT-594 GPEC Review

# August 21, 2001

ABB T31519

EXHIBIT  
Page 23  
1022091

**EXHIBIT**  
McCarthy  
54  
929-0626



## ABT-594 August 2001 GPEC Review

- Development Update Bruce McCarthy
- DSG Analysis Steve Kuemmerle  
Liz Kowaluk
- NNR Follow-ons Michael Meyer

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## ABT-594 August 2001 GPEC Review Topics

- ABT-594 efficacy in neuropathic pain is significant
  - ABT-594 has a narrow therapeutic window and efficacious doses are poorly tolerated as dosed currently
  - Modifications to drug administration have the potential to improve tolerability
- Decision analysis suggests that the expected value for these modifications (to improve tolerability) is small, although positive
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

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## ABT-594's Potential for Pain Relief

- Efficacy across preclinical models of pain
  - Efficacy of morphine without morphine-like adverse events
  - Efficacy in neuropathic pain
- Commercial and clinical development plan targeted acute and chronic nociceptive pain and neuropathic pain, based upon preclinical promise
- Tolerability/onset of action issues made neuropathic pain relatively more attractive
  - Dosages that provide meaningful acute relief of pain are not well tolerated
  - Titration not well suited to intermittent use, as seen with most chronic nociceptive pain
  - Titration is used with all currently available drugs for neuropathic pain

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**ABT-594 GPEC Review:  
Diabetic Neuropathic Pain Phase  
IIIb Study Results (M99-114)**

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## Phase IIb Study in Neuropathic Pain (M99-114)

### *Study Results*

- Summary
- Neuropathic pain reminder
- Study Design
- Efficacy Results
- Adverse Events
- Conclusions and Options

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## M99-114 Neuropathic Pain

### Summary

- **EFFICACY**
  - 150, 225 and 300 mcg BID are significantly better than placebo as measured by the primary efficacy variable (reduction in daily pain)
 

• ITT Analysis:	29-30%	vs. 17% placebo
– Gabapentin:	39%	vs. 22% placebo
• Completer Analysis:	38-48%	vs. 18% placebo
• Responder rates:	26% (ITT), 47% (Completer)	
  - Greater mean pain reduction and responder rates in site-based pain measurements
- **TOLERABILITY & SAFETY**
  - Dose dependent increase in nausea, vomiting, dizziness
 

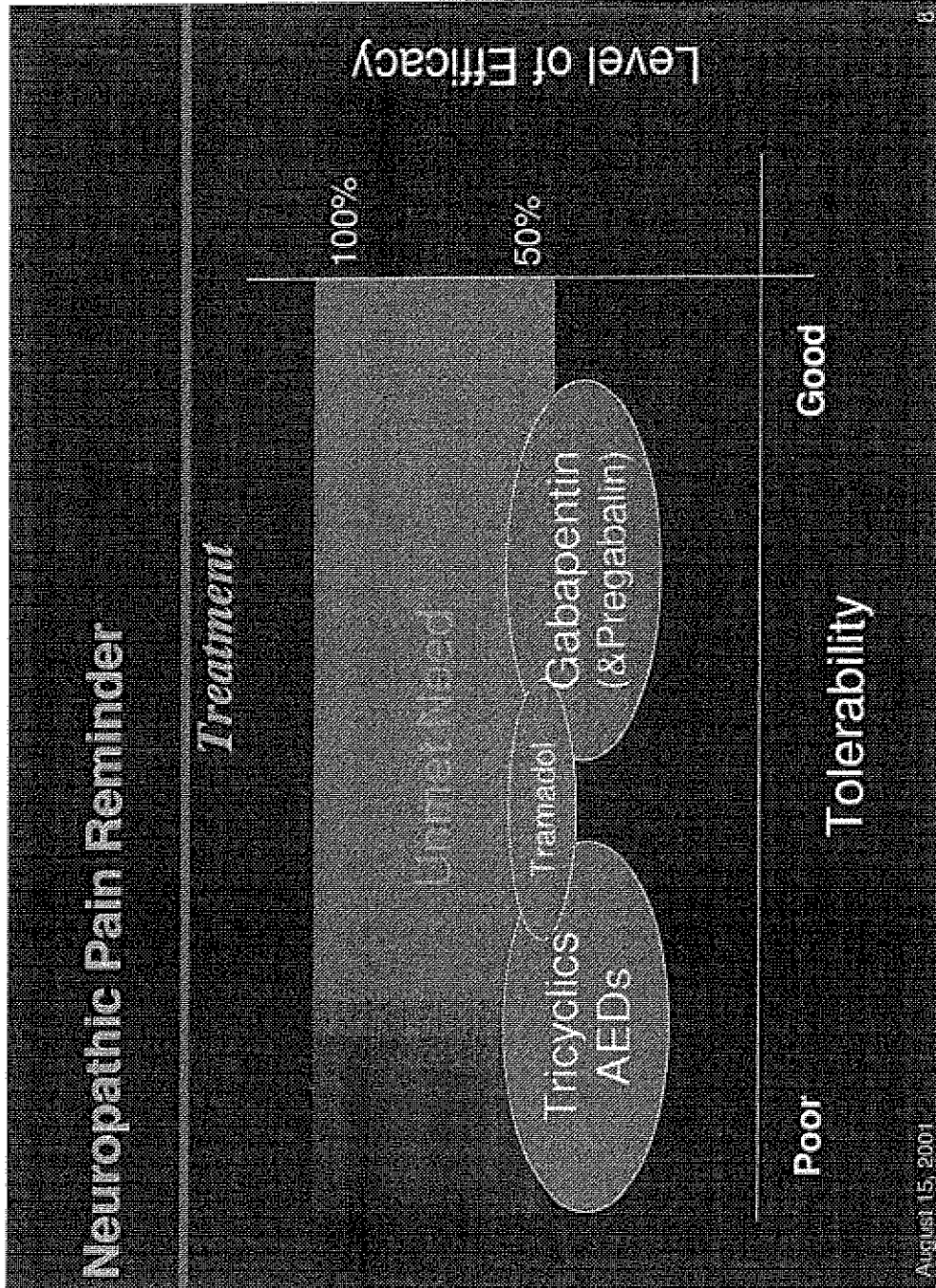
• Nausea:	34-46%	• Dizziness:	17-28%
• Vomiting:	15-21%	• Abnormal Dreams:	18-22%
  - Significant Discontinuation Rate: 66% due to AE at 300 mcg BID

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## Neuropathic Pain Market

	2000 Rx (MM)	2000 sales (\$MM)	Rx CAGR (96-2000)	Sales CAGR (96-2000)
Total:				
US	10.6	\$470	6%	45%
Ex-US	18.1	\$235	11%	24%
Gabapentin				
US	3.9	\$352	80%	94%
Ex-US	1	\$42	125%	191%

Source: Decision Resources; IMS factored analysis.

- Growth of sales for neuropathic pain agents exceeds Rx growth.
- Driven by continued growth of the branded and premium priced gabapentin (Neurontin), at the expense of other anti-epileptics and generic tricyclic antidepressants.

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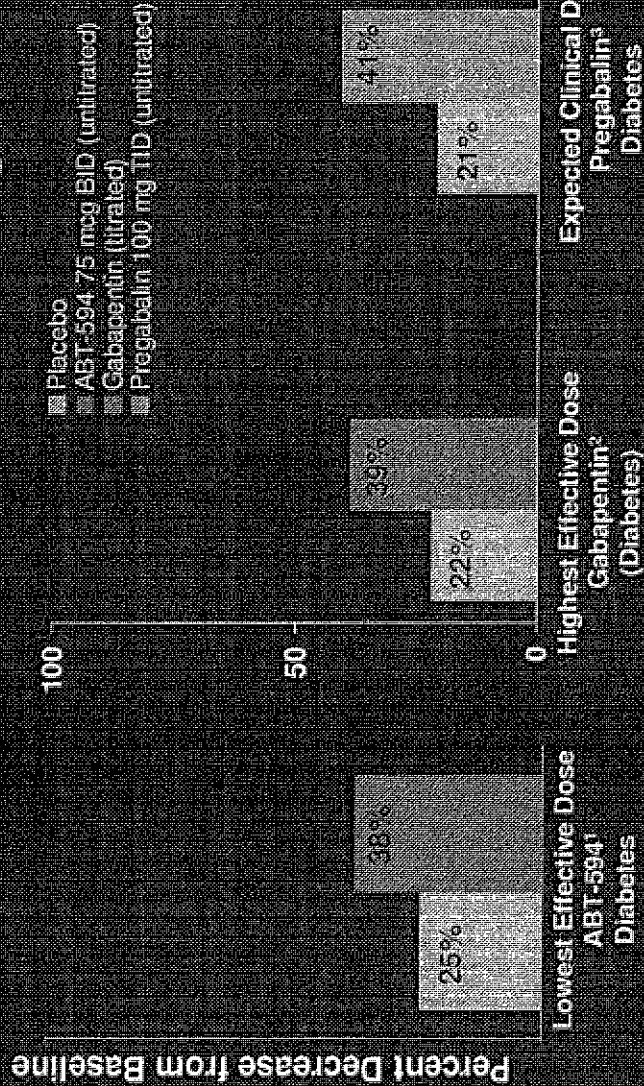
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# Phase IIa: ABT-594 75 mcg BID Had a Similar Effect To Gabapentin

## ABT-594 vs. Gabapentin and Pregabalin



<sup>1</sup> 4-point categorical scale final vs. baseline  
<sup>2</sup> 11-point Likert Scale week 8 vs. baseline  
<sup>3</sup> 11-point Likert scale week 5 vs. baseline

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## Phase IIa: ABT-594 75 mcg BID Untitrated Was Relatively Well Tolerated

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

<sup>1</sup> Max. 1987 (n=20)

<sup>2</sup> M98-826 and M98-833 combined

N/A - Not Available

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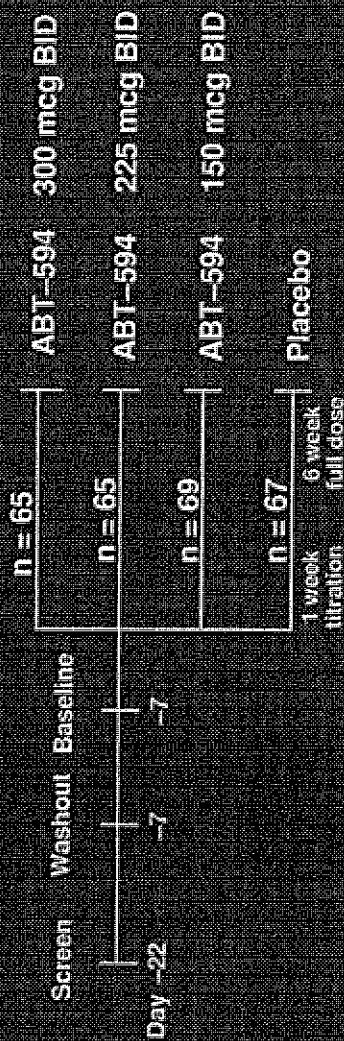
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## Phase IIb Neuropathic Pain (M99-114)

### Design

- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-day titration phase; treatment visits at 2, 3, 5 and 7 weeks
- Power
  - Planned: 80% for ES 0.46 with 20/group
  - Study: 60% for ES 0.46 with 56/group (ES 0.55 for site-based pain rating scale)
- Concomitant analgesics disallowed

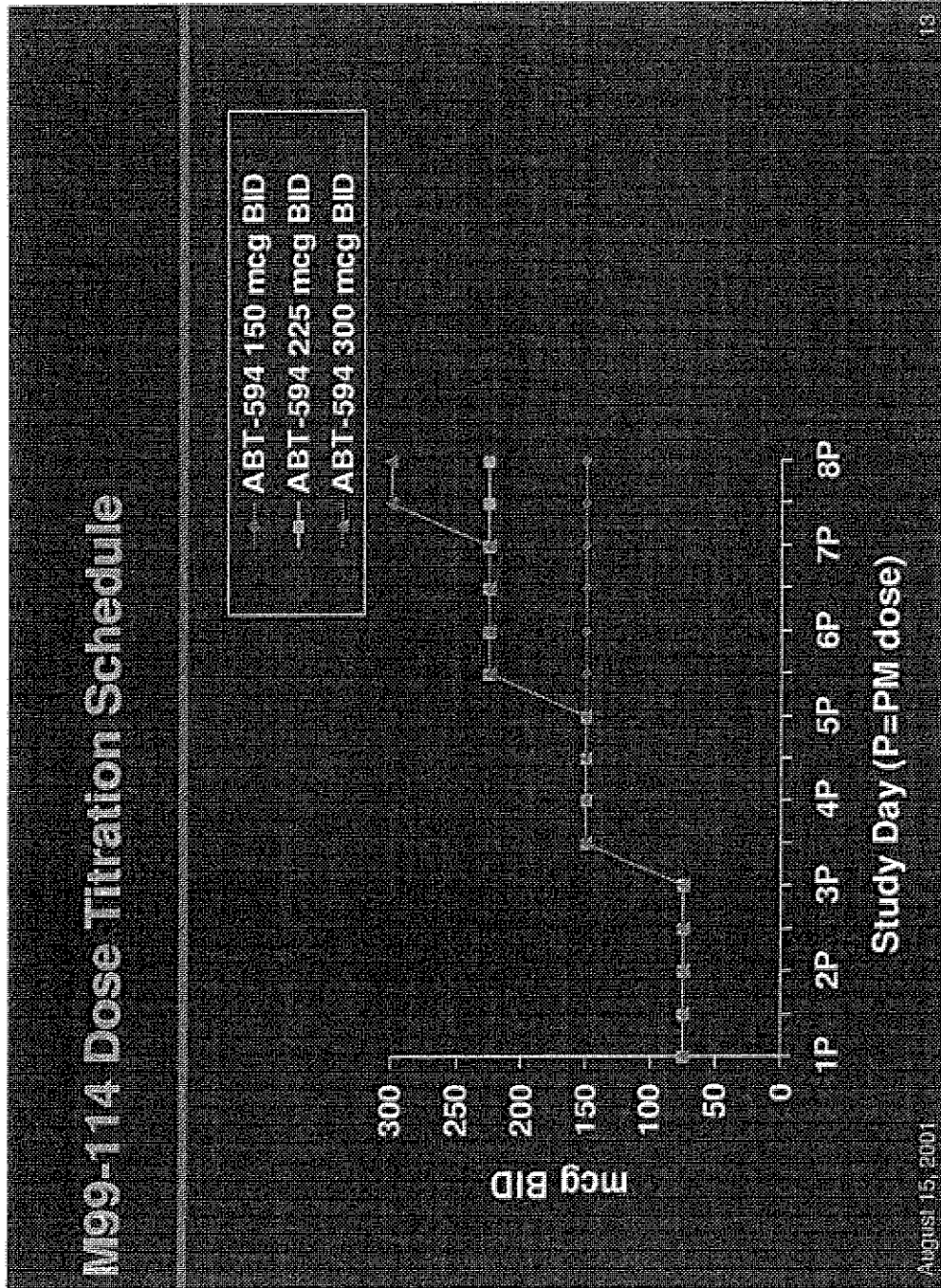
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# Premature Terminations Increased with Increasing doses of ABT-594

## *Subject Disposition*

Reason for Discontinuation	Placebo	% of Subjects Discontinuing ABT-594		
		150 mcg BID	225 mcg BID	300 mcg BID
Adverse Event	9	28	46	66
Lack of Efficacy	9	9	3	7
Lost to Follow-up	0	0	1	3
Withdrew Consent	3	5	9	7
Other	2	2	4	3
Total Discontinuation	22	38	57	75

Percents may not sum correctly due to rounding

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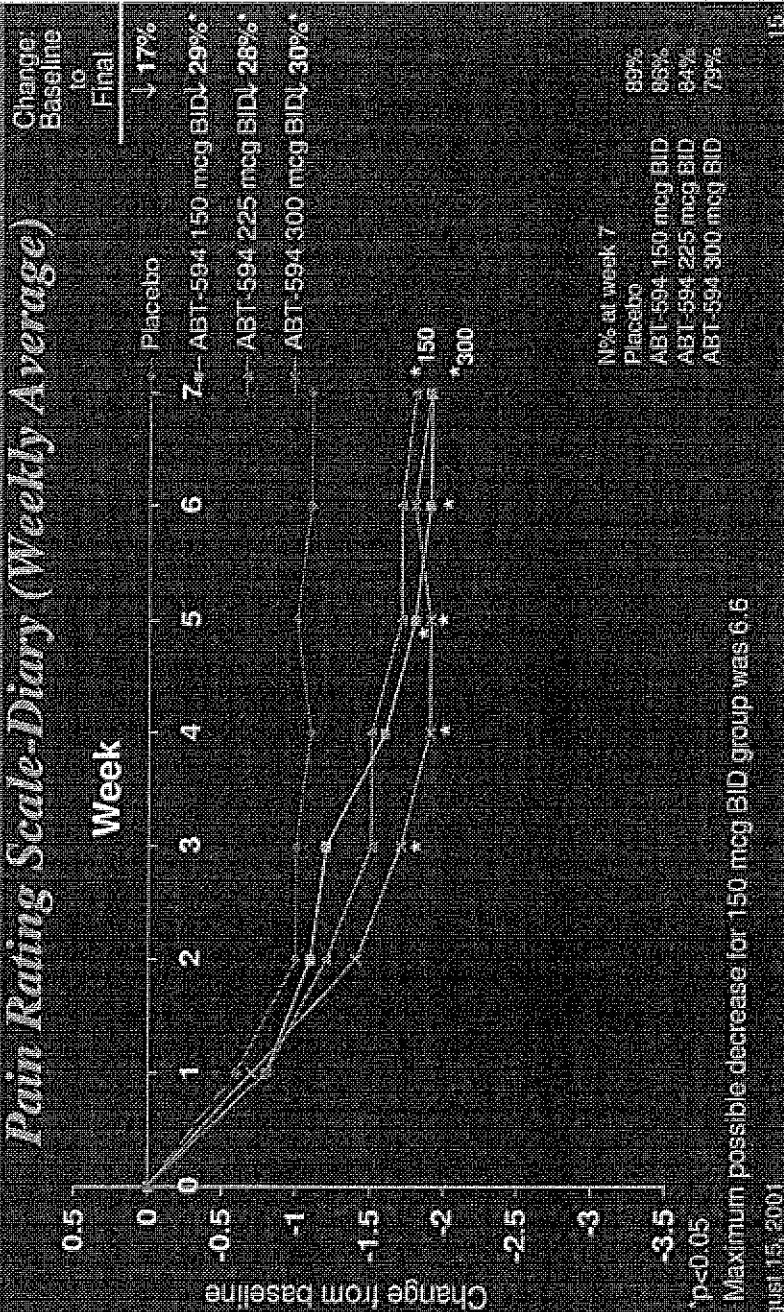
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**ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by the Primary Efficacy Variable: Intent to Treat Population**


### *Pain Rating Scale-Diary (Weekly Average)*




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**Completer Analysis May Predict Upside Potential of ABT-594**



**ITT**



**Completer**

*Advantages*

Scientific evaluation of study results

Potential to predict upside of efficacy if all patients were able to complete study

*Disadvantages*

Handicapped prediction of upside potential of efficacy given high discontinuation rate (especially early)

Patients who completed the Phase IIb study may not predict accurately efficacy if all patients could tolerate ABT-594

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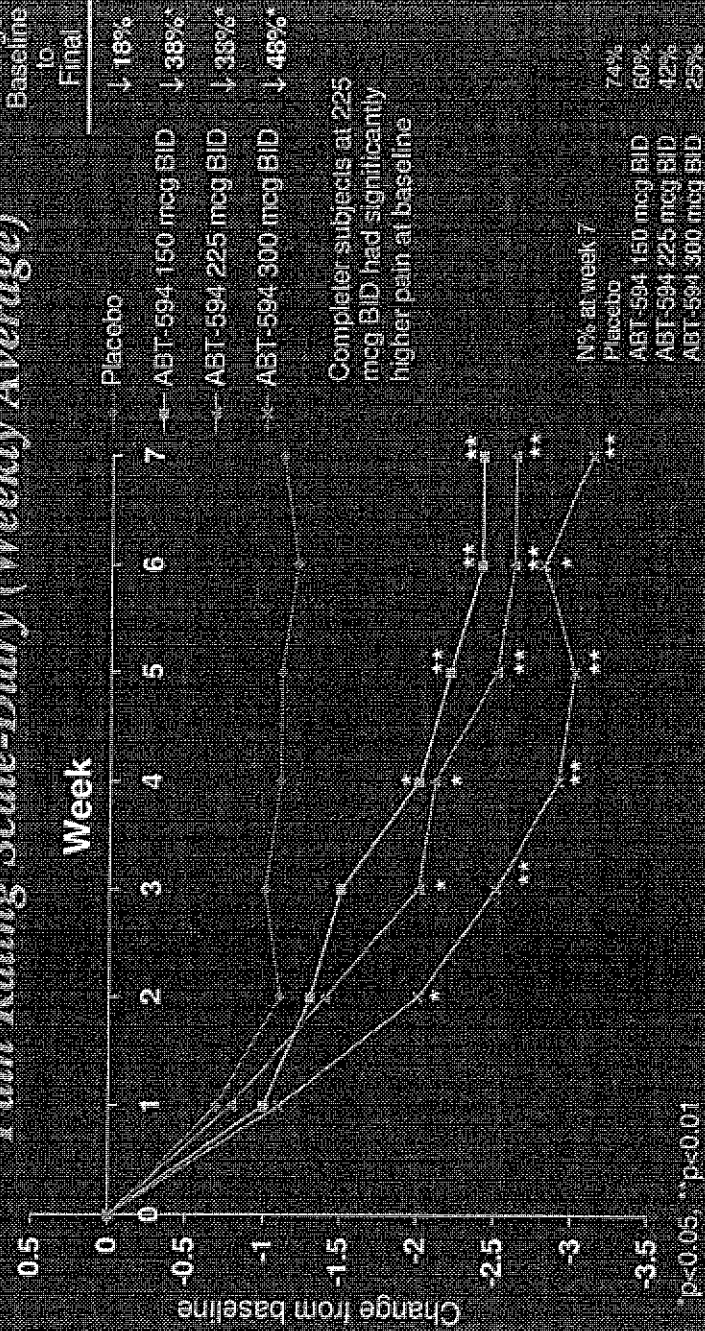
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## D's Exhibit 661 – Part 2



ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by the Primary Efficacy Variable: subjects who completed study

### Pain Rating Scale-Diary (Weekly Average)



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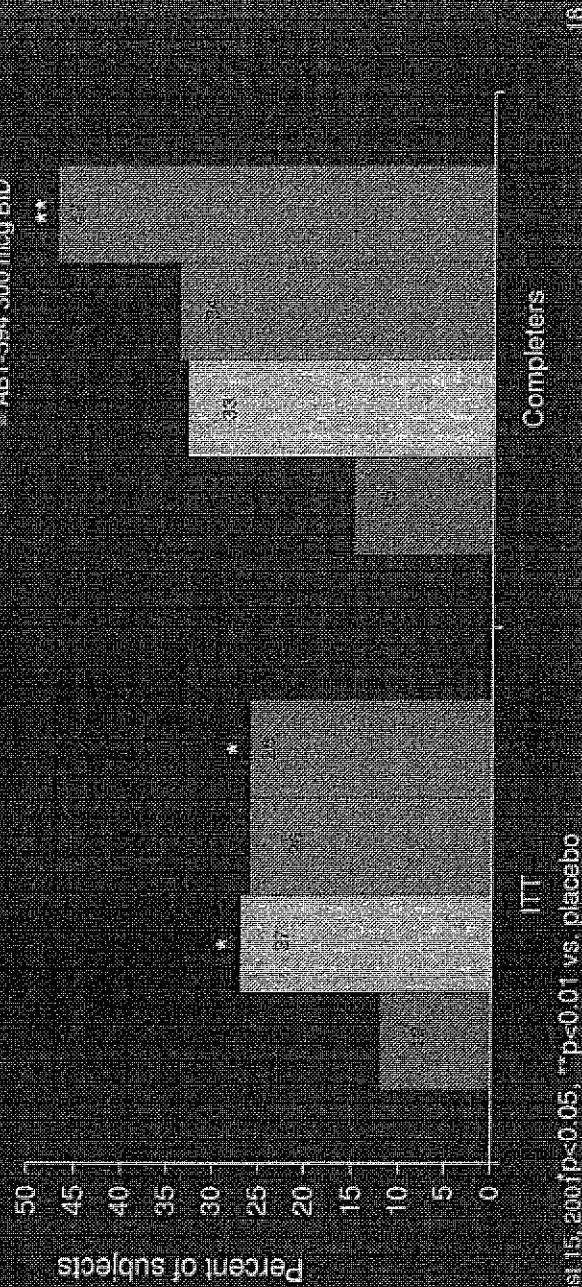
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# **Responder Rates 50% or greater improvement**

## *Pain Rating Scale-Diary*

- Placebo
- ABT-594 150 mg BID
- ABT-594 225 mg BID
- ABT-594 300 mg BID



August 15, 2007 p<0.05, \*\*p<0.01 vs. placebo

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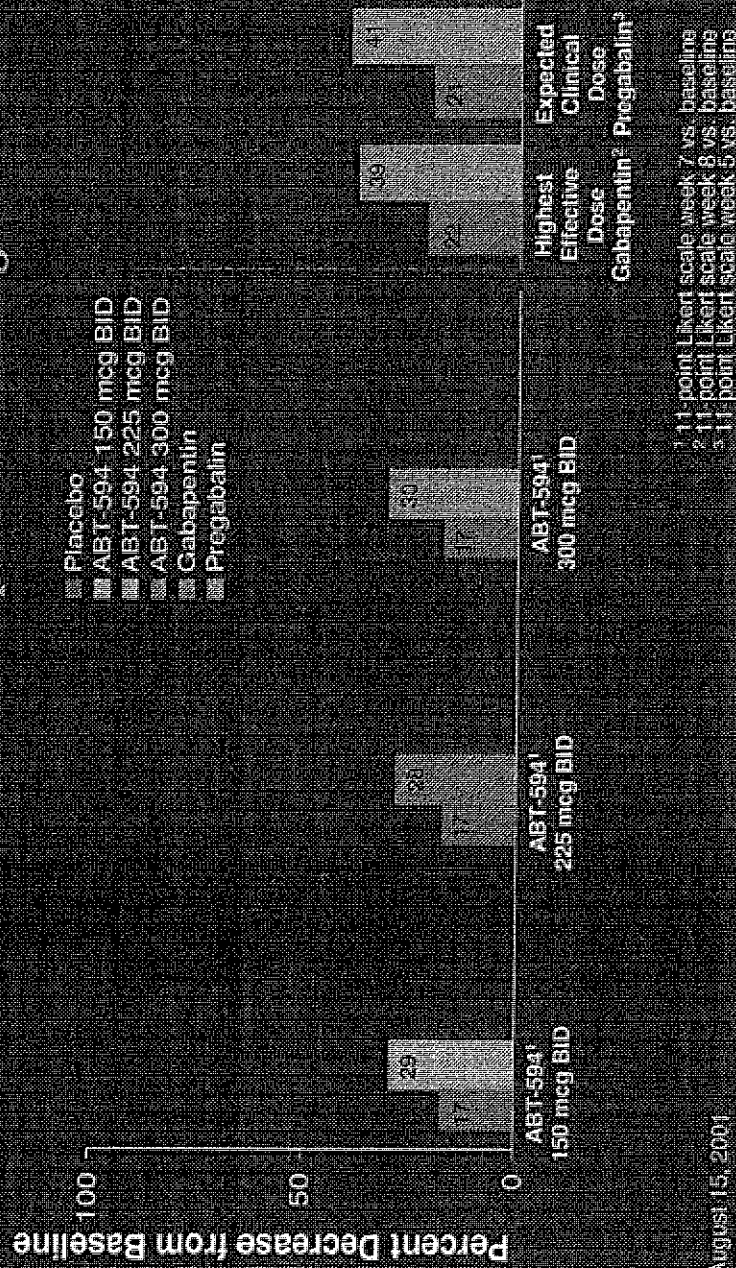
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# **ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain More than Gabapentin or Pregabalin**

## ***ABT-594 ITT vs. Gabapentin and Pregabalin***



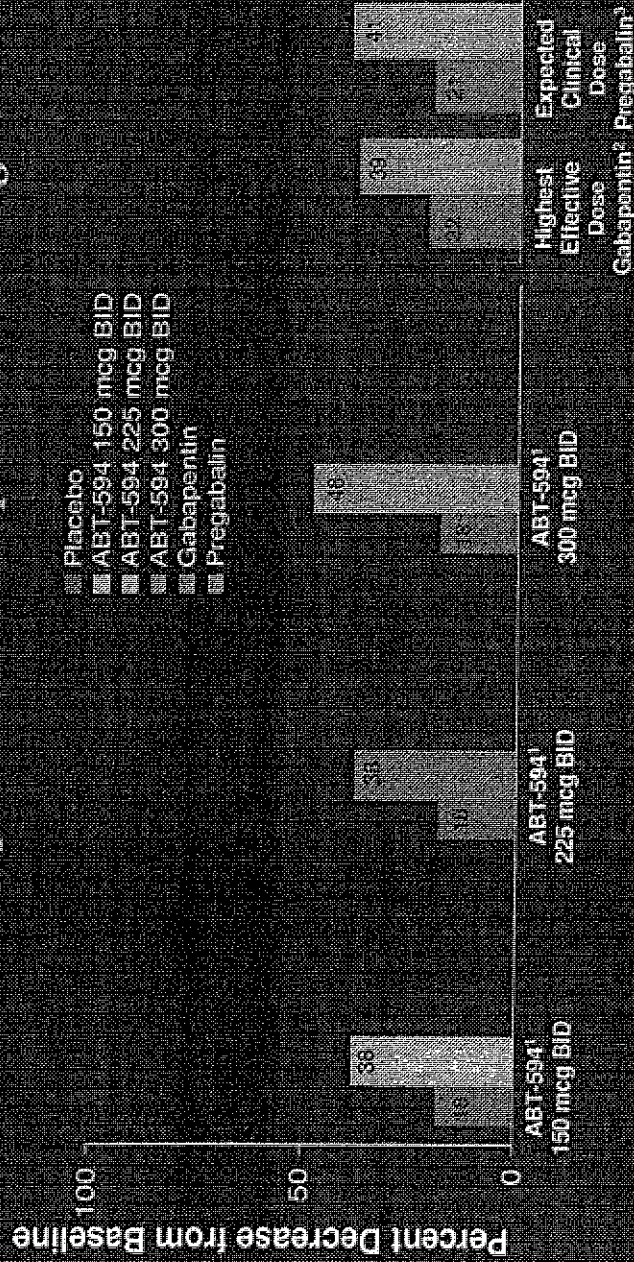
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# ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain More than Gabapentin or Pregabalin

## ABT-594 Completers vs. Gabapentin and Pregabalin



<sup>1</sup> 11-point Likert scale week 7 vs. baseline  
<sup>2</sup> 11-point Likert scale week 8 vs. baseline  
<sup>3</sup> 11-point Likert scale week 5 vs. baseline

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## Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d <sup>1</sup>	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 150 mcg BID	ABT-594 300 mcg BID
Confusion	N/A	8%	5%	0%	1%
Somnolence	66%	23%	24%	2%	0%
Dizziness	28%	24%	27%	17%	28%
Nausea	N/A	8%	N/A	34%	46%
Vomiting	N/A	N/A	N/A	15%	21%
Peripheral edema	N/A	N/A	7%	0%	0%
Constipation	14%	N/A	N/A	3%	7%
Dry mouth	50%	N/A	N/A	3%	1%

<sup>1</sup> Max, 1987 (n=29)  
N/A - Not Available

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**Efficacy and safety did not vary meaningfully by  
subject characteristics**

- Smoker/Non-smoker
- Male/Female
- Weight
- Age
- Renal Function

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ABT-594 150, 225 and 300 mcg BID Were Not Associated with Clinically Meaningful Changes in Vital Signs, ECGs or Laboratory Data

- Vital signs
- ECG
- Laboratory data

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## M99-114: Neuropathic Pain

### *Conclusions*

- ABT-594 significantly reduces diabetic neuropathic pain
- ABT-594, as administered without additional improvements in tolerability, has a narrow therapeutic window
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

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## ABT-594 Options

- A: Attempt tolerability improvement with ABT-594
  - Explore more prolonged titration
  - Co-administer anti-emetic
  - Protocol Ready
    - 7, 11, 21 day titrations
    - Co-administered anti-emetic
    - Detailed assessments of adverse events
    - \$2.8 MM Fully burdened VERIFY
- B: No additional experiments with ABT-594
  - Subtype selective NNR for pain back-up

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## **Rationale for Titration and/or co-administration of an anti-emetic to improve tolerability of ABT-594**

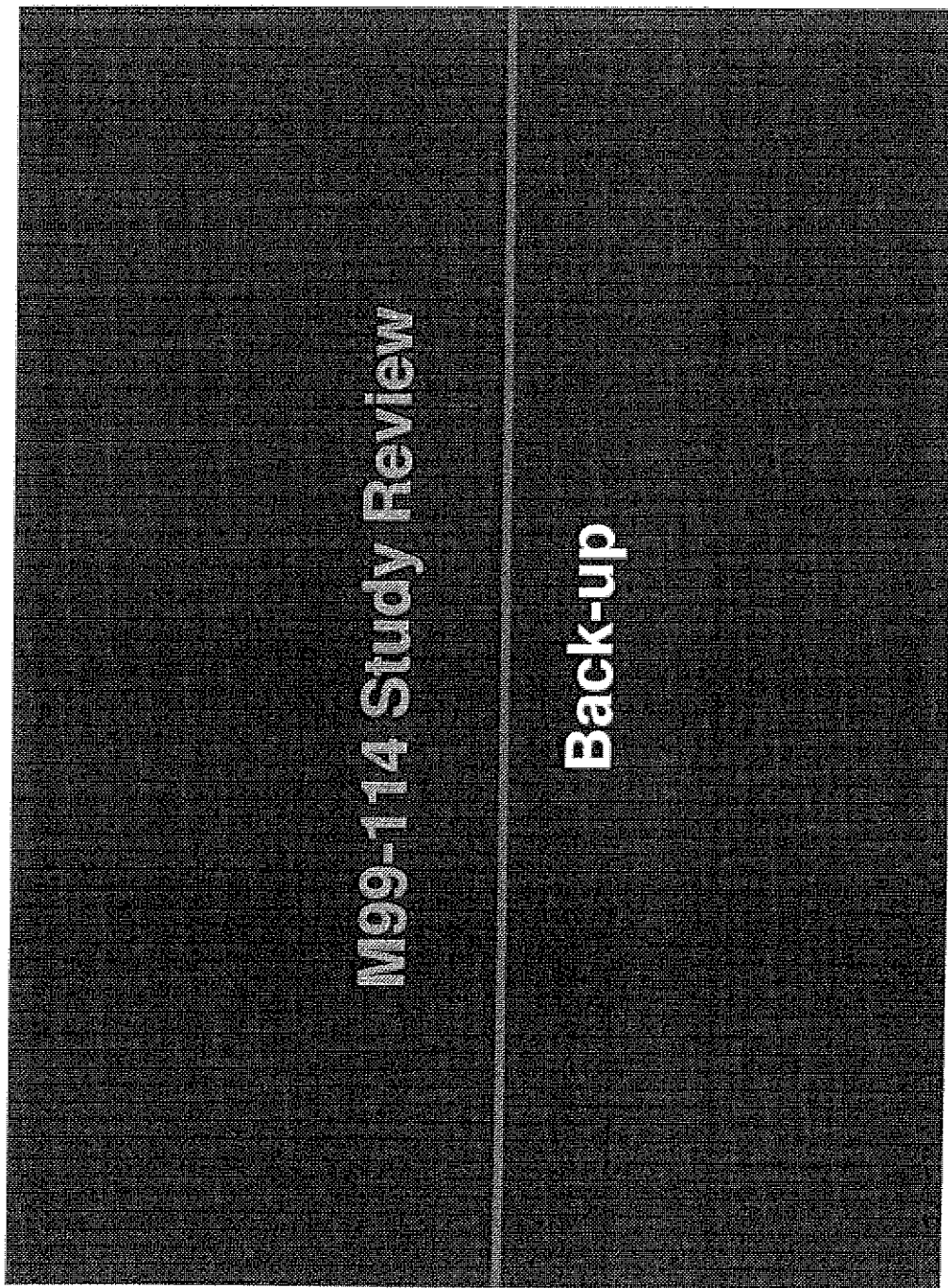
- Titration
  - General hypotheses
    - Adverse event tolerance
    - Homeostasis
  - Evidence
    - Attenuation of AEs over time in earlier studies, especially doses  $\leq 75$  mcg BID
    - Preclinical evidence of attenuation over time
    - Titration is used to improve the tolerability of most analgesic, neurological and psychiatric Drugs
- Anti-emetic
  - Suppression of priming effect during tolerance/homeostasis
  - Preclinical studies
    - Dopamine antagonists
    - 5-HT<sub>3</sub> antagonists

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## M99-114: Neuropathic Pain

### *Outcome Measures*

- **Primary**
  - Weekly average of daily Pain Rating Scale (11-point Likert in a diary)
    - Change from baseline to last 7 days on drug
- **Secondary**
  - Site-based Pain Rating Scale (11-point Likert)
  - Neuropathic Pain Scale
  - Patient Global Impression of Change
  - Clinician Global Impression of Change
  - SF-36

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## M99-114: Neuropathic Pain

### Outcome Measures

#### • Pain Rating Scale

**PRIMARY**

0	1	2	3	4	5	6	7	8	9	10
no pain										
					worst pain possible					

#### • Neuropathic Pain Scale (NPS)

– 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10
The most sharp sensation imaginable ('like a knife')										

#### • Subject, Clinician Impression of Change

- |   |                     |
|---|---------------------|
| 1 | Much Improved       |
| 2 | Moderately Improved |
| 3 | Minimally Improved  |
| 4 | No Change           |
| 5 | Minimally Worse     |
| 6 | Moderately Worse    |
| 7 | Much Worse          |

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## Opinion Leader Comments on ABT-594 Results

- Russ Portenoy
- Howard Fields
- Martin Koltzenburg

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## ABT-594 Tolerability Improvement Study

- Controlled, randomized, double-blind, placebo-controlled Phase I
- Adequately powered
- Five Groups:
  - Placebo
  - 7 Day titration  $\pm$  anti-emetic up through steady state
  - 11 Day titration
  - 24 Day titration

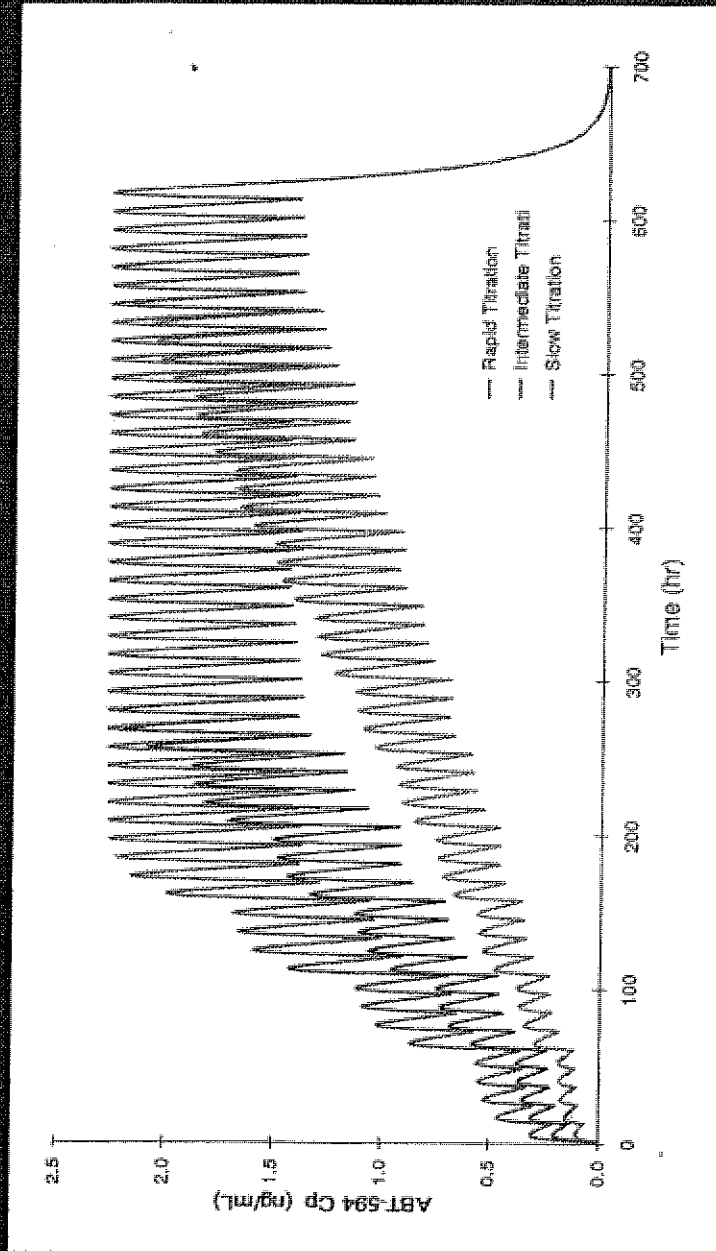
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## ABT-594 Tolerability Improvement Study



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## Titration Is Used to Improve the Tolerability of Most Analgesic, Neurological and Psychiatric Drugs

### *Tramadol in naïve patients: Ruoff Study*

	1 Day to 200 mg/day n=130	4 Days to 200 mg/day n=129	10 Days to 200 mg/day n=132
Nausea	29%	31%	21%
Vomiting	10%	12%	8%
Dizziness	24%	19%	8%
Discontinuation Due to AEs	31%	24%	15%

- Patients with chronic joint pain treated with daily NSAIDs and requiring additional pain relief.

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## Titration Is Used to Improve the Tolerability of Most Analgesic, Neurological, and Psychiatric Drugs

### *Tramadol in intolerant patients: Petrone Study*

	10 Days to 200 mg/day n=54	16 Days to 200 mg/day n=59	13 Days to 150 mg/day n=54
Nausea	54%	42%	33%
Vomiting	19%	12%	7%
Dizziness	7%	7%	7%
Discontinuation Due to AEs	54%	34%	30%

- Patients who had discontinued due to nausea or vomiting during a rapid escalation of tramadol dose (4 days to 200 mg/day) were enrolled in the titration evaluation.
- Patients with chronic pain treated with daily NSAIDs.

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# Meyer Deposition Exhibit 23

## D's Exhibit 661 – Part 3



## Hypotheses for ABT-594-induced Emesis

- Parenteral administration also elicits emesis in preclinical studies
- No models exist to determine the relative contribution of central and peripheral actions of ABT-594 in emesis

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## ABT-594 Parenteral

- An option to evaluate different rates-of-rise under single dose administration
- Additional preclinical experiments required
  - More fully explore safety of different rates-of-rise
  - Parenteral drug safety studies
- Formulation development
- Time & Cost
  - EST 6 months
  - EST \$ 0.5 MM

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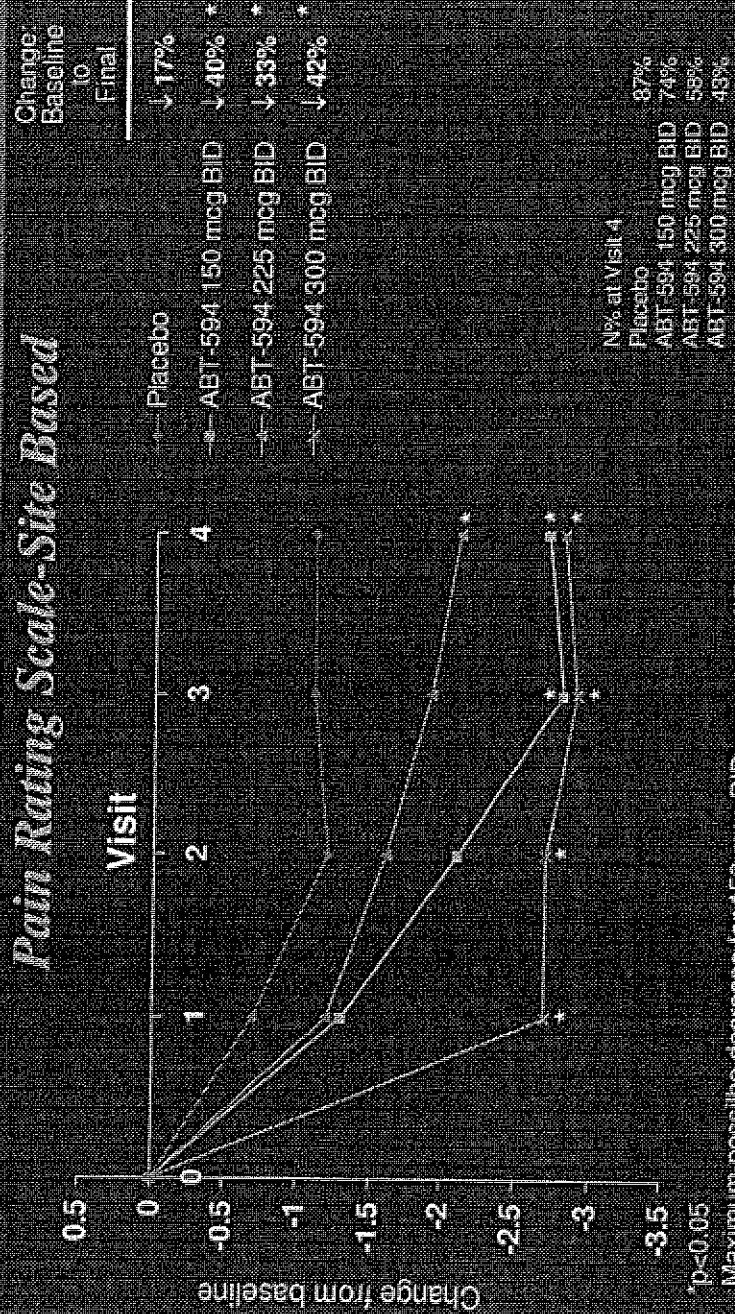
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**ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale: Intent to Treat Population**

### *Pain Rating Scale-Site Based*



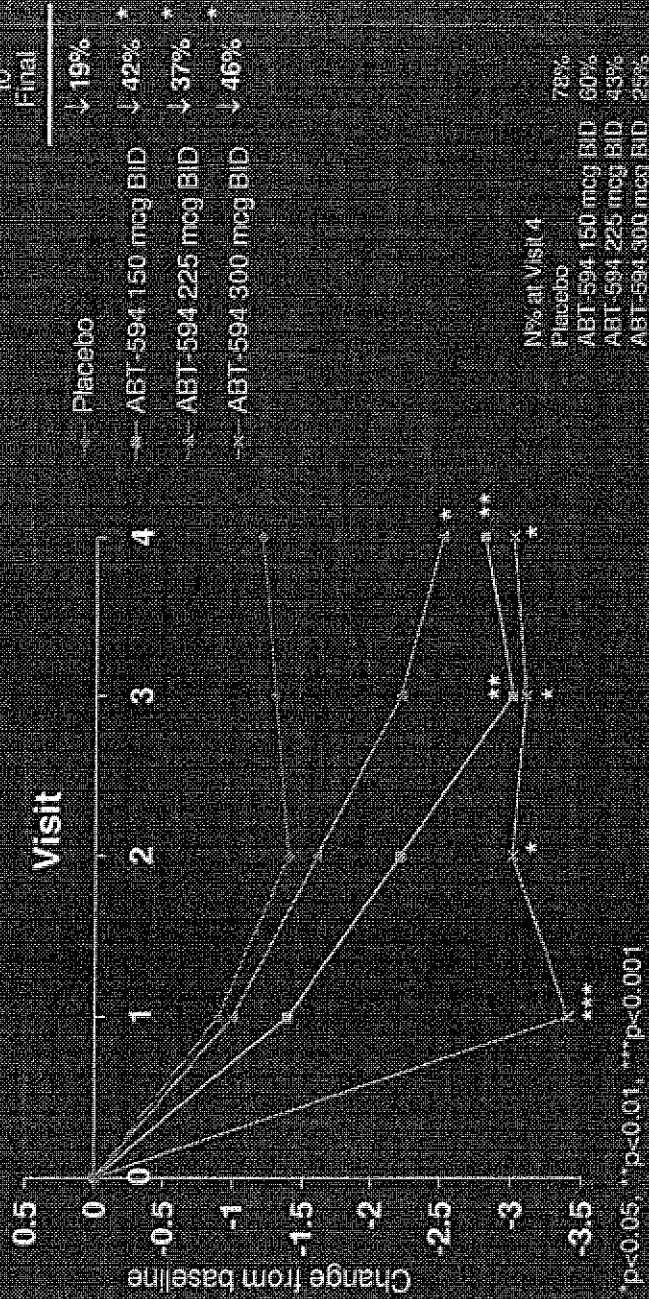
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ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale: subjects who completed study

### Pain Rating Scale-Site Based



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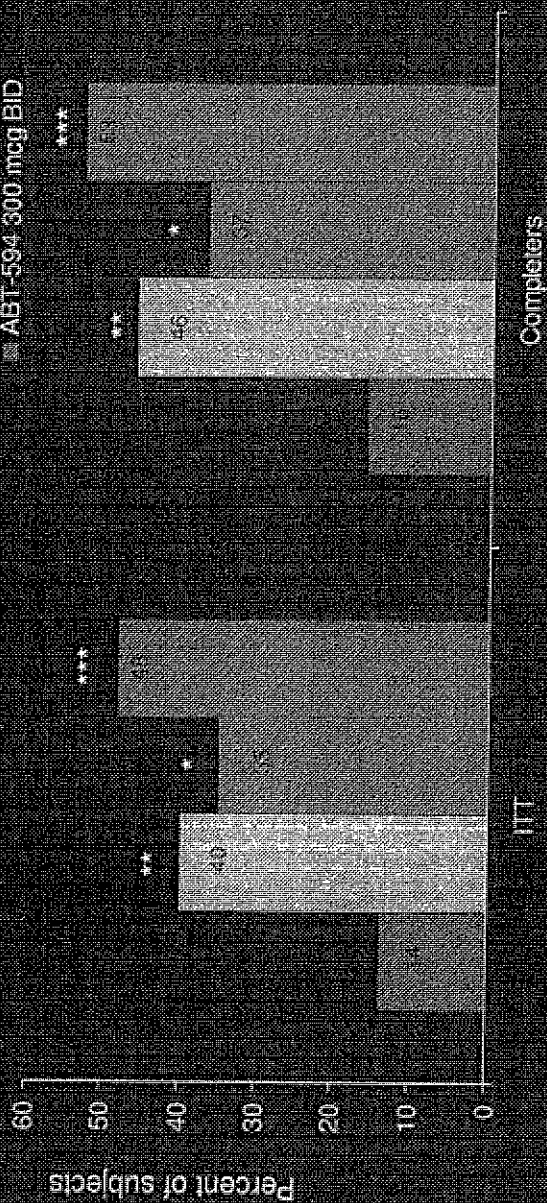
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# **Responder Rates 50% or greater improvement**

## *Pain Rating Scale-Site*

- Placebo
- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID



August 15, 2001 \*\*\*p<0.001, \*\*p<0.01, \*\*\*p<0.001 vs. placebo

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## M99-114 Neuropathic Pain

### *Summary*

- **Initial Questions**
  - Where do doses evaluated to date fit on the dose-response curve?
    - PK/PD effect?
  - Can tolerability be improved?
    - Differentiation of patient populations
    - Dosage administration
  - If tolerability is improved, will there be even more efficacy?
  - How much will patients benefit from ABT-594?
    - If administered as in M99-114
    - Given hypothetical improvements in tolerability & efficacy
- **Conclusions**
  - ABT-594 significantly reduces diabetic neuropathic pain
  - ABT-594, as administered without any optimization, has a narrow therapeutic window
  - ABT-594 has the potential to be an important treatment for neuropathic pain; additional analyses will evaluate the probability that differentiation of patient populations or changes in dosage administration can improve therapeutic index

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## ABT-594 IS A MAJOR SCIENTIFIC ACHIEVEMENT

- *Independent of future business decisions regarding ABT-594...*

- ABT-594 is the first drug ever to be successfully discovered and developed with the intent purpose to treat neuropathic pain (and other pain disorders).
- NNRS are now fully validated as a viable mechanism to treat neuropathic pain
- For the first time in decades there is now an additional class of analgesic agents:

- **NNRS**
- OPIOIDS
- NSAIDS/COX-2s
- ACETAMINOPHEN
- TCAs/AEDs

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Treatment Groups Were Similar in Terms of Demographics at Baseline

### *M99-114 Baseline Characteristics*

		All Patients (N=266)
Gender	Female	45%
	Male	55%
Race	White	89%
	Black	9%
Age	Mean	62
	Range	20-86
Weight	Mean	202
	Range	112-278
Nicotine Use	Former	36%
	Never	53%
	Current	11%

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Treatment Groups Were Similar in Terms Pain at Baseline

*M99-114 Baseline Characteristics*

	Placebo	ABT-594 150 mcg BID	ABT-594 225 mcg BID	ABT-594 300 mcg BID
Pain Rating Scale Diary (10)	6.5	6.6	6.7	6.7
Pain Rating Scale Site (10)	6.5	6.7	6.7	6.9
Neuropathic Pain Scale (100)	56.5	55.1	56.3	57.3

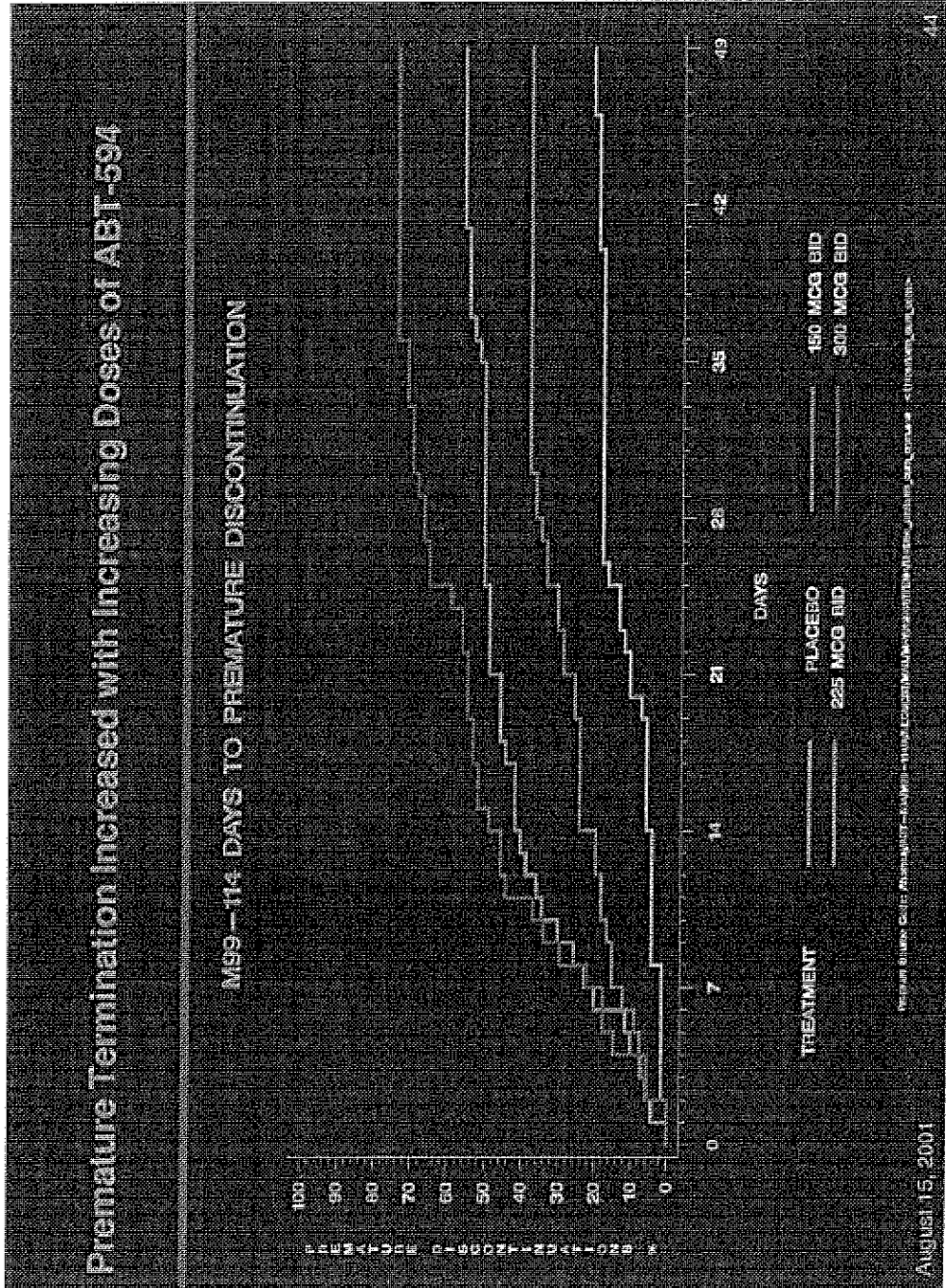
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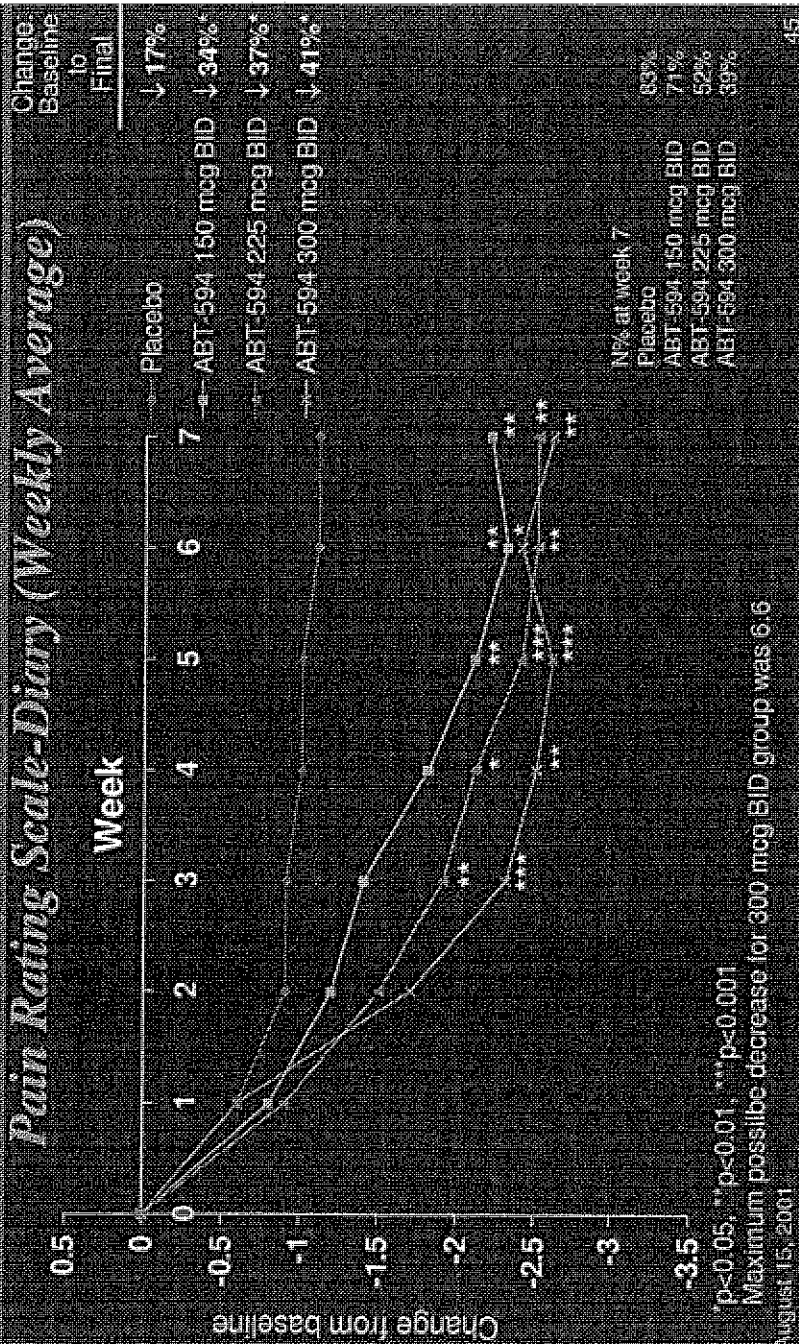


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ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by the Primary Efficacy Variable: subjects who complete at least 21 days

### Pain Rating Scale-Diary (Weekly Average)



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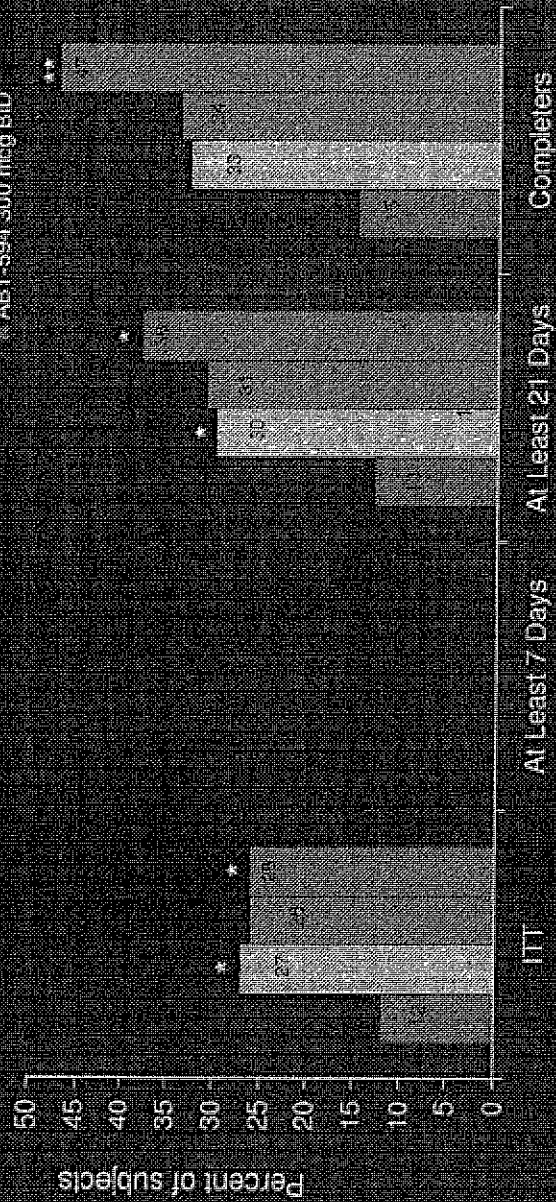
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# **Responder Rates 50% or greater improvement**

## *Pain Rating Scale-Diary*

- Placebo
- ABT-594 150 mg BID
- ABT-594 225 mg BID
- ABT-594 300 mg BID

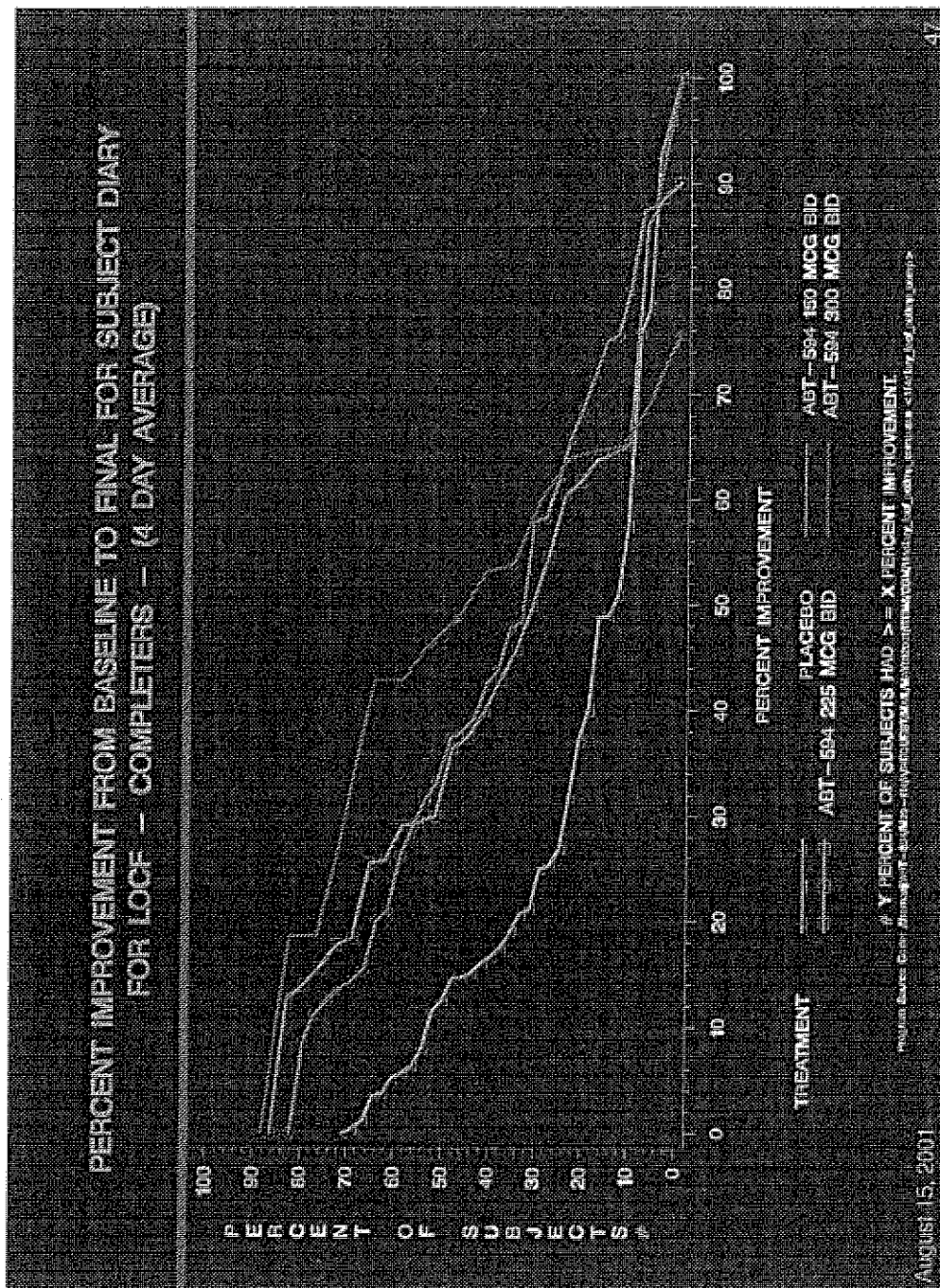


August 15, 2007 P<0.05

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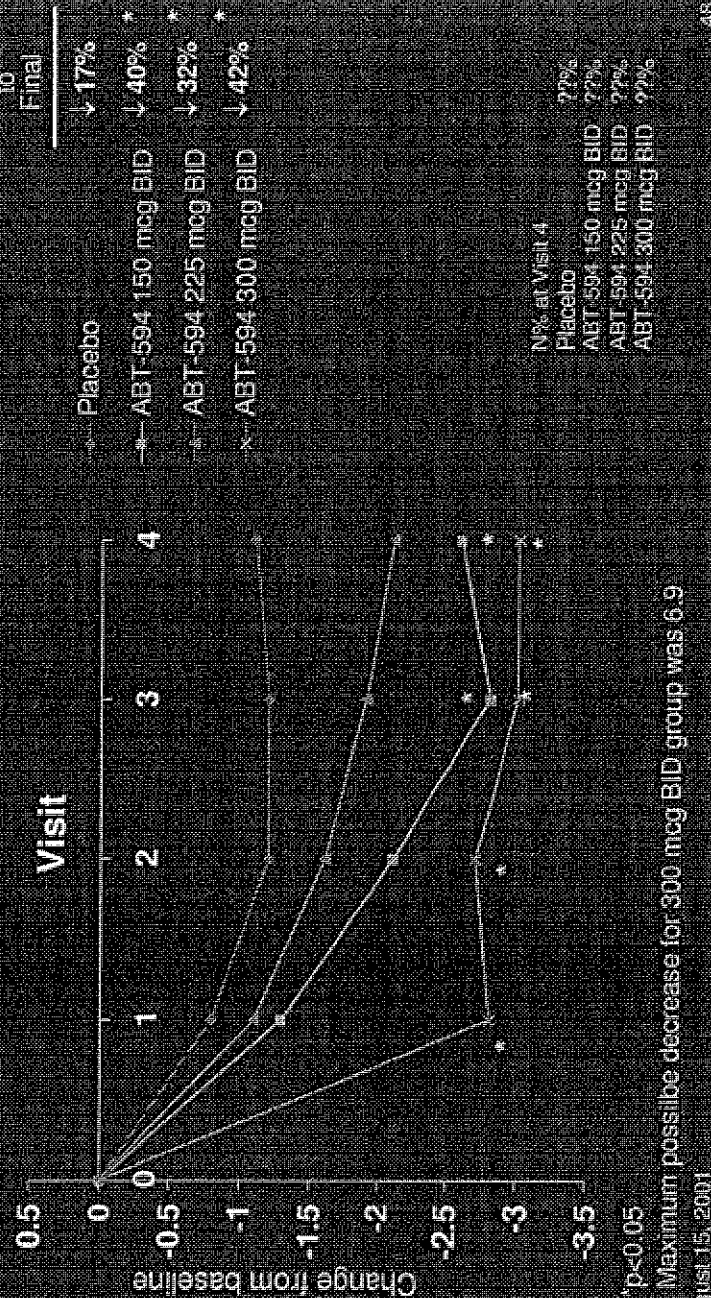
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ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale: subjects who complete at least 21 days

### Pain Rating Scale (Site Based)



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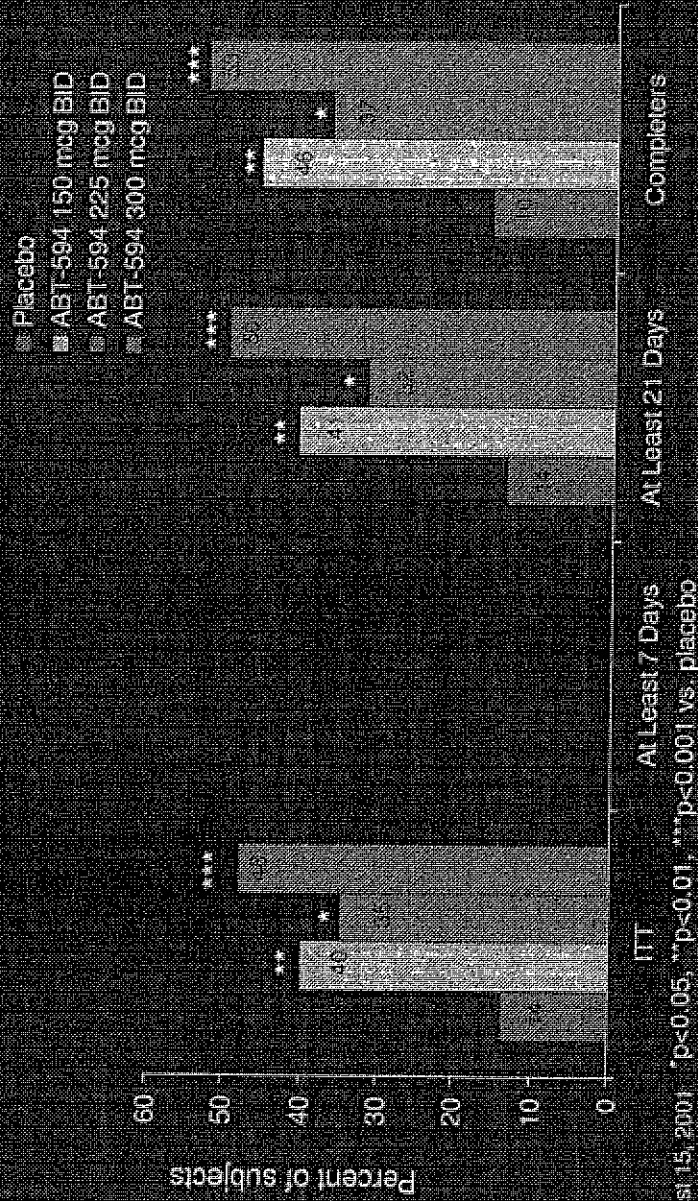
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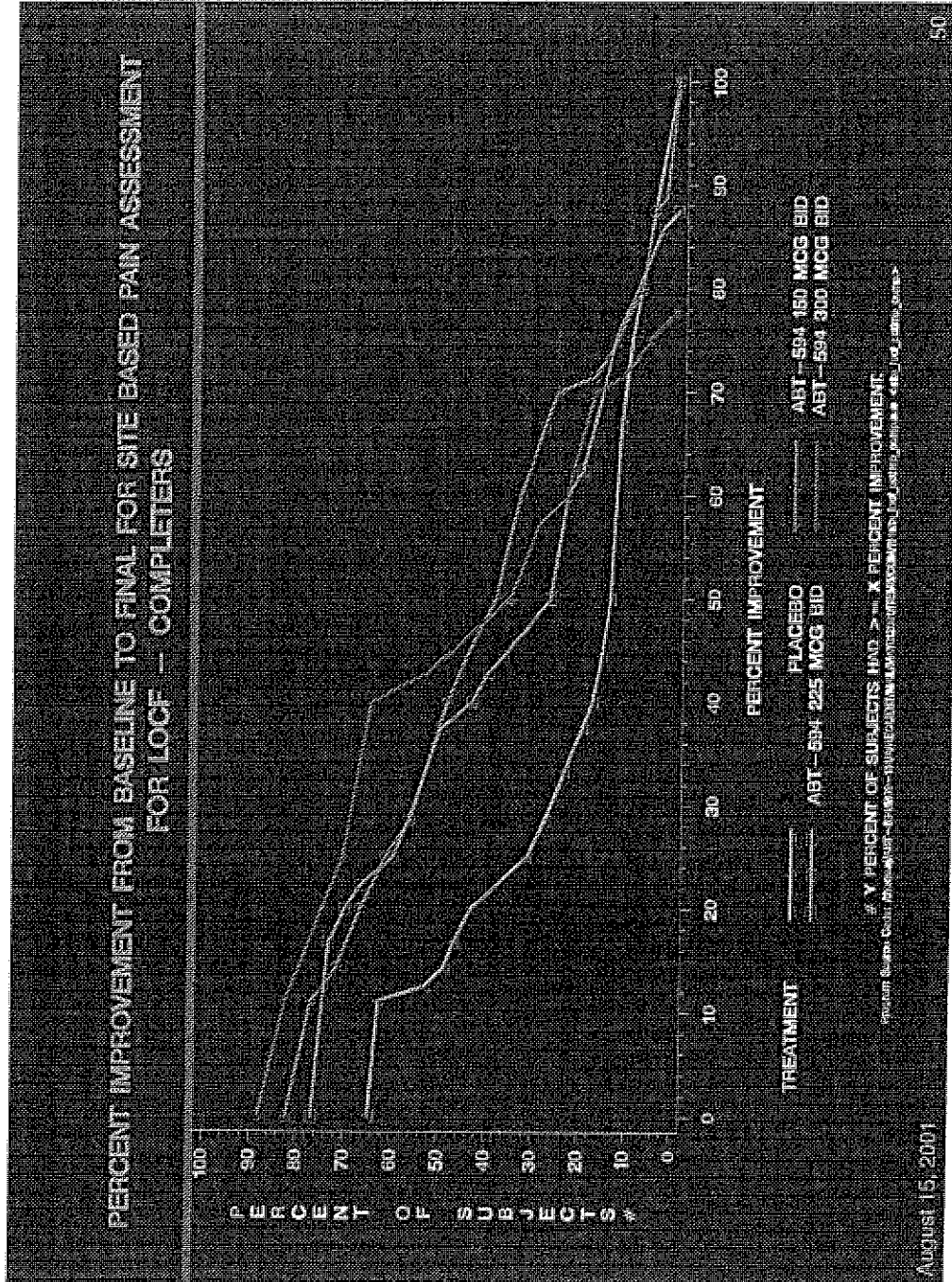
# **Responder Rates 50% or greater improvement**

## *Pain Rating Scale-Site*



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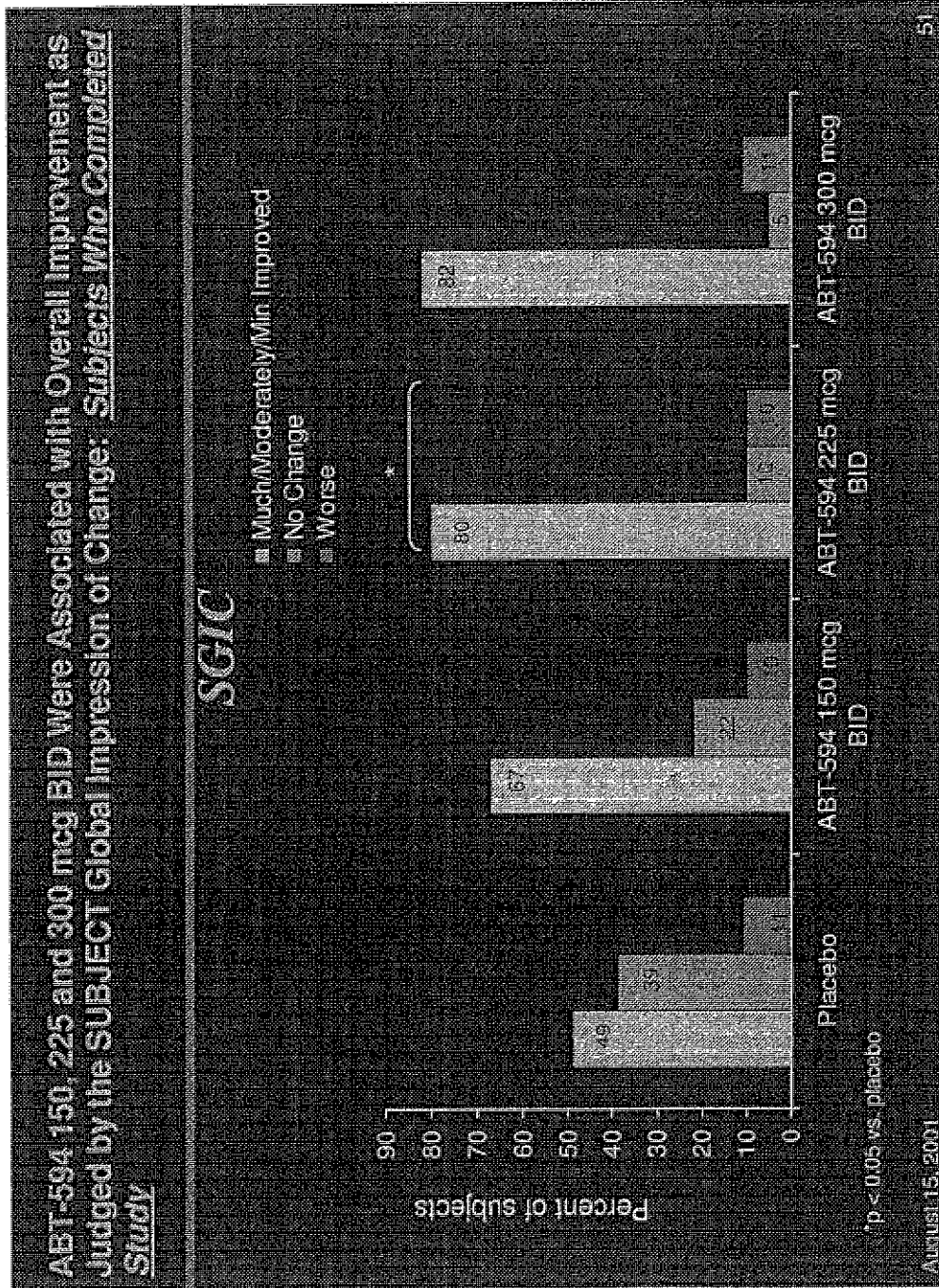
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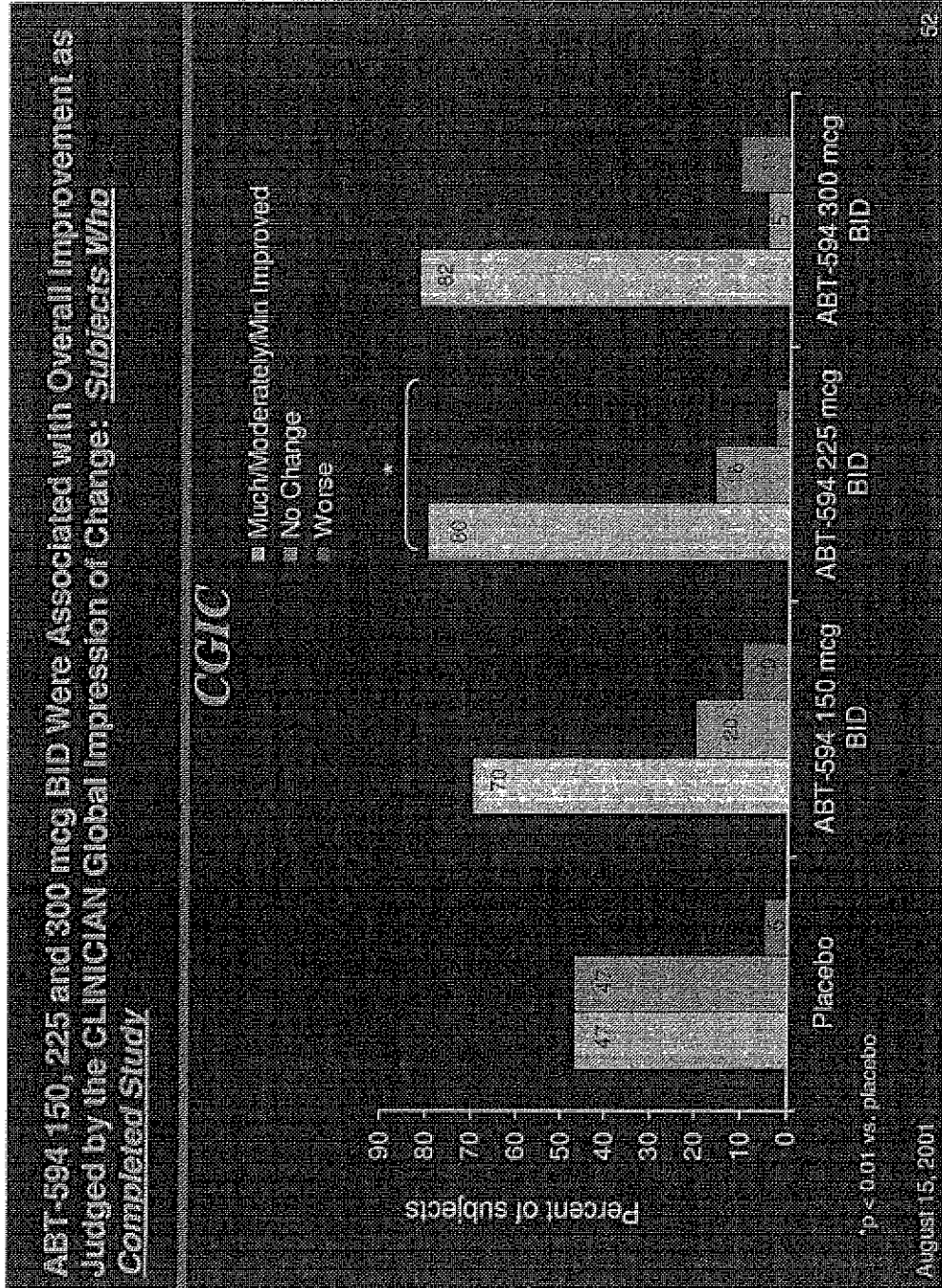
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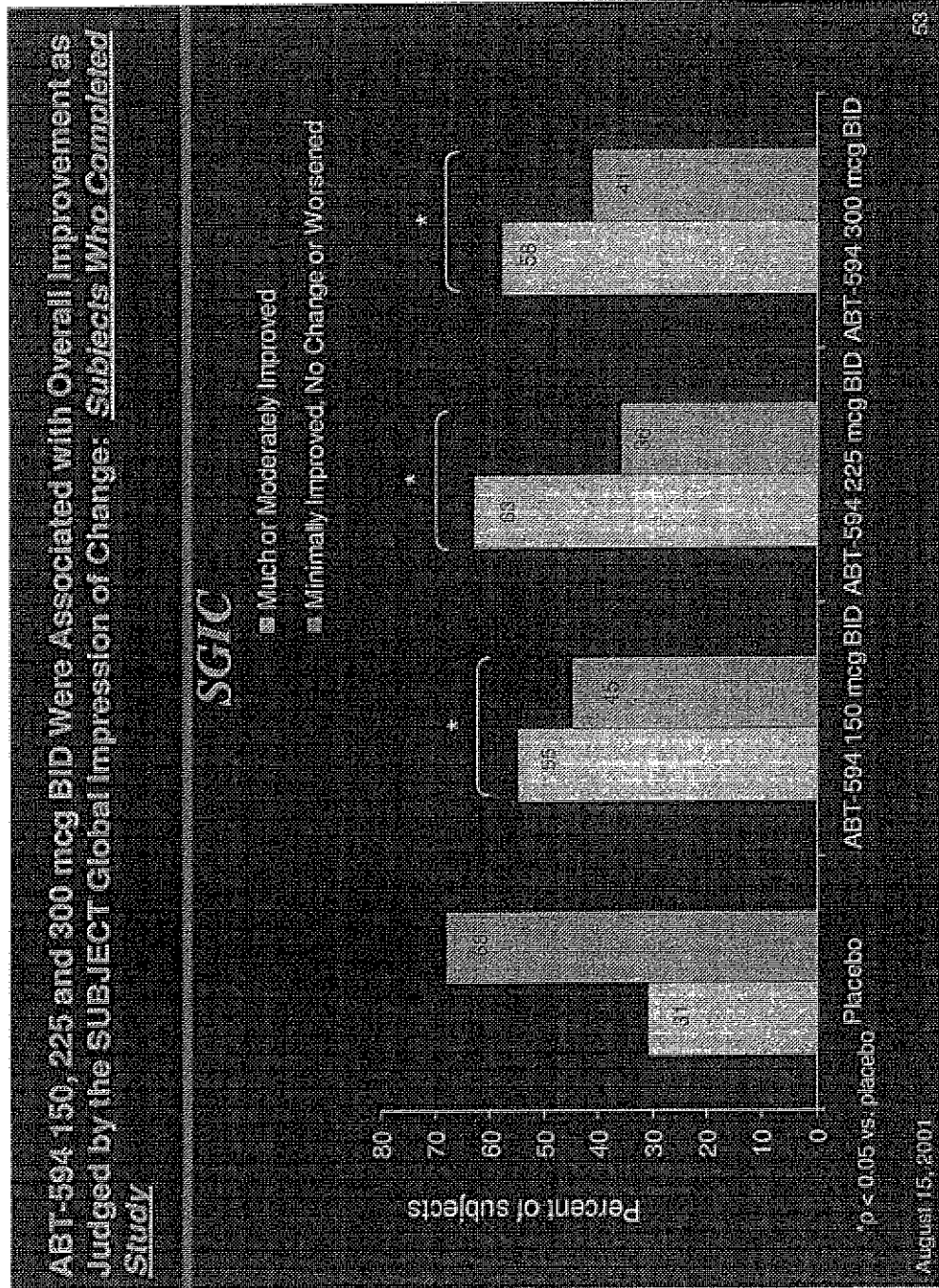
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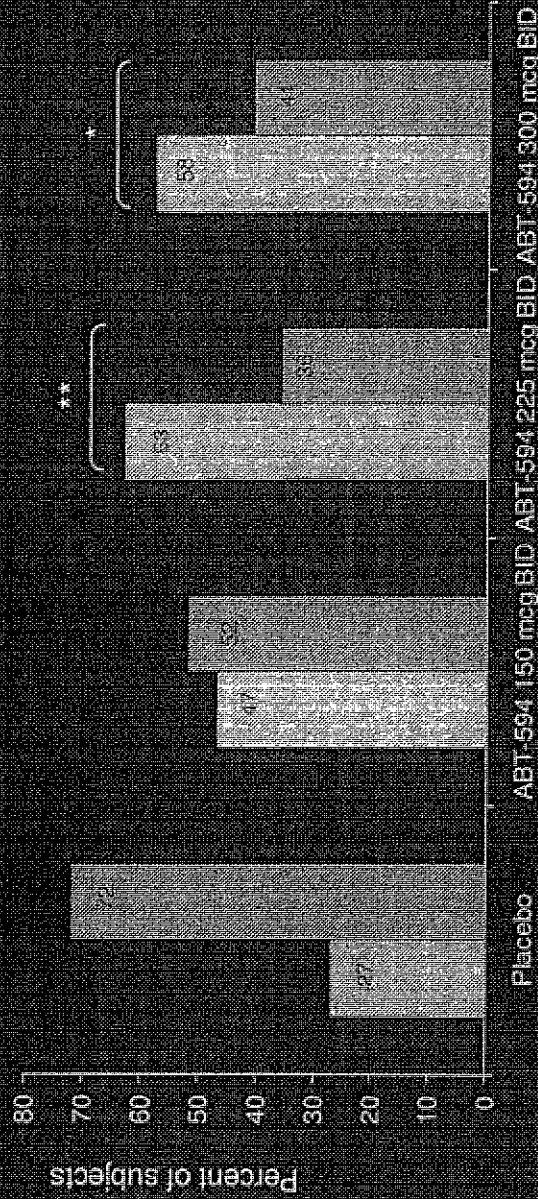
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**ABT-594 150, 225 and 300 mcg BID Were Associated with Overall Improvement as Judged by the CLINICIAN Global Impression of Change: Subjects Who Completed Study**

**CGIC**

- Much or Moderately Improved
- Minimally Improved, No Change or Worsened



\*p < 0.05; \*\* p < 0.01 vs. placebo

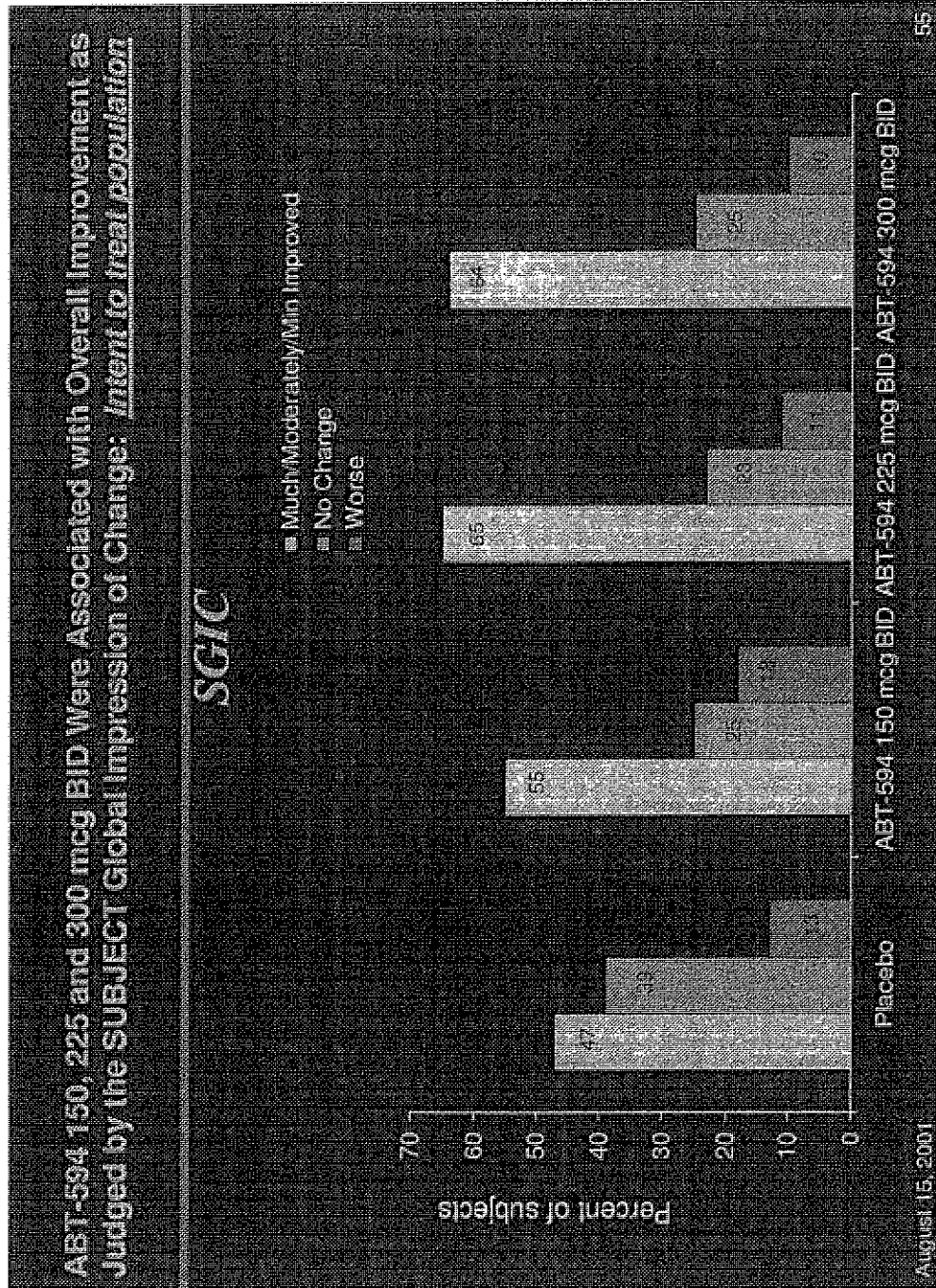
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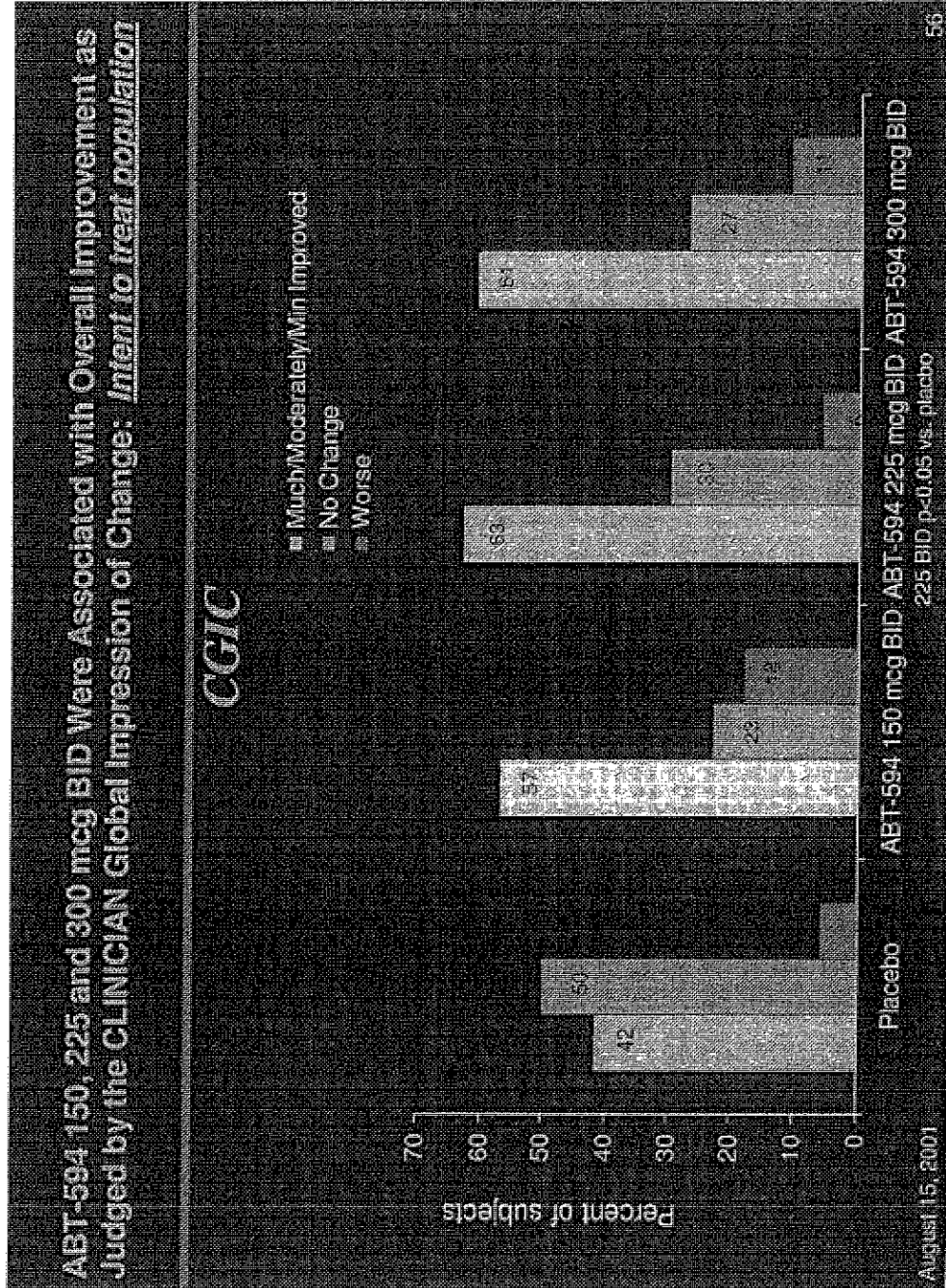
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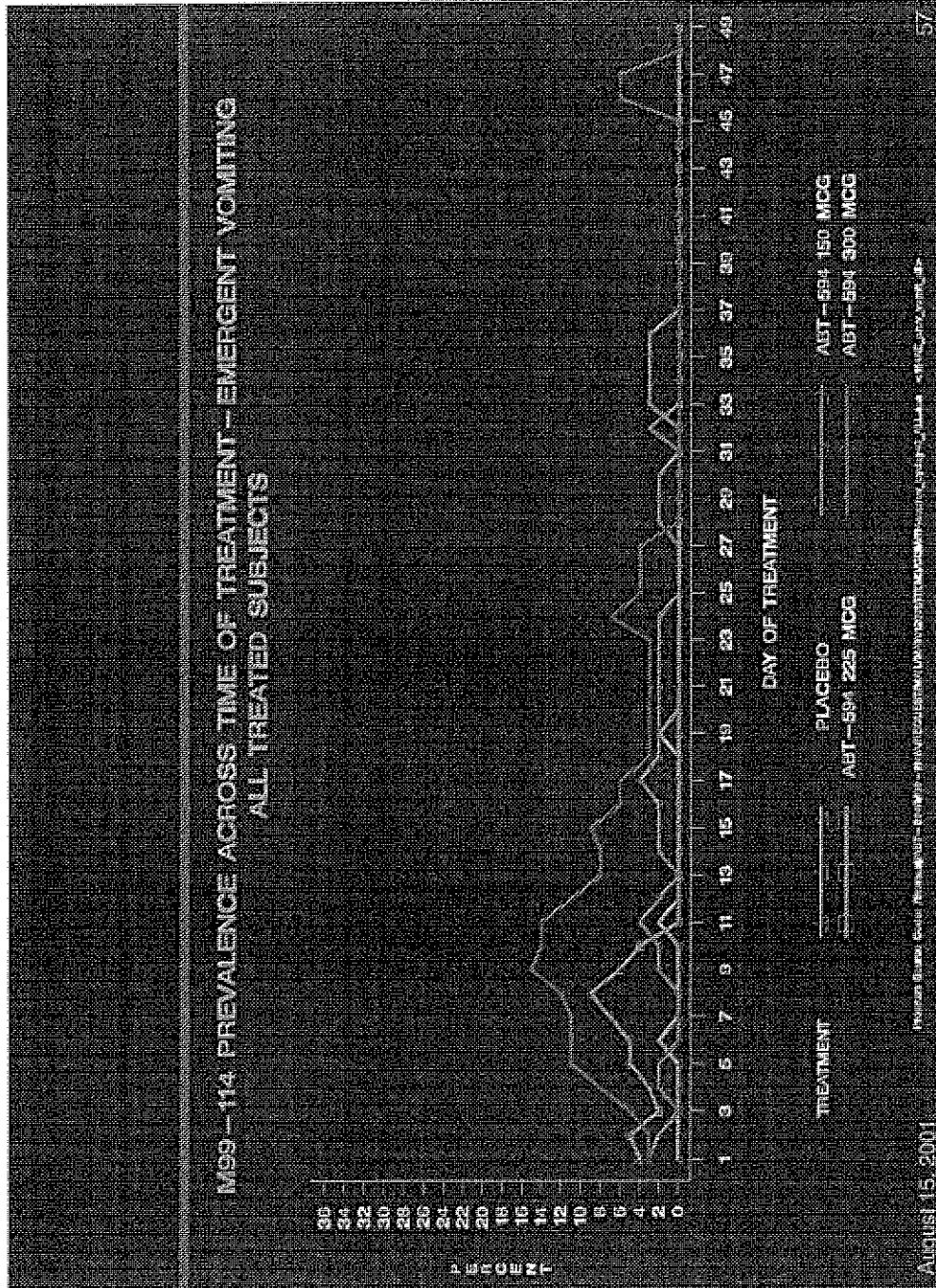
ABBT311573



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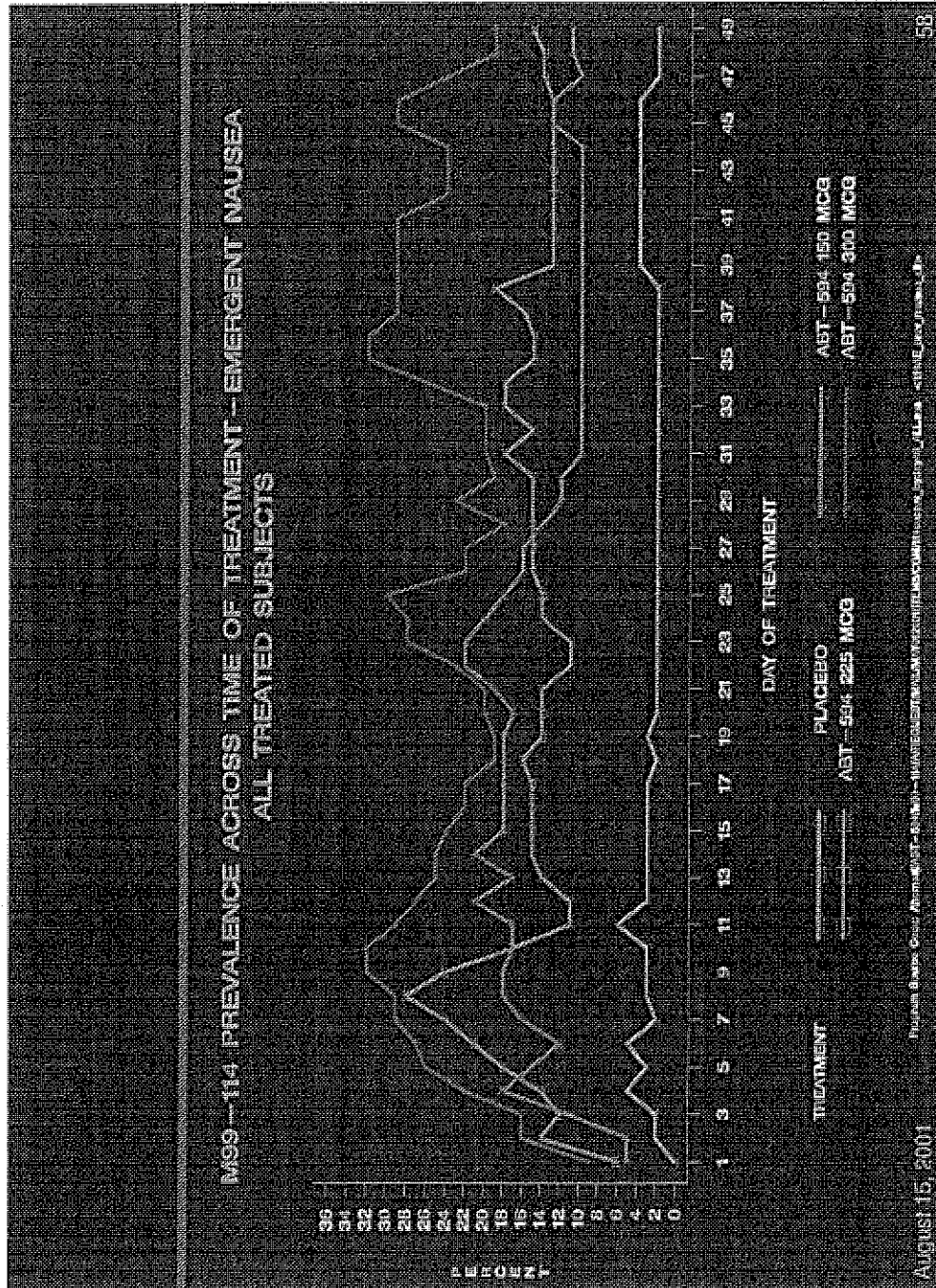
ABBT311574





ABBT311575

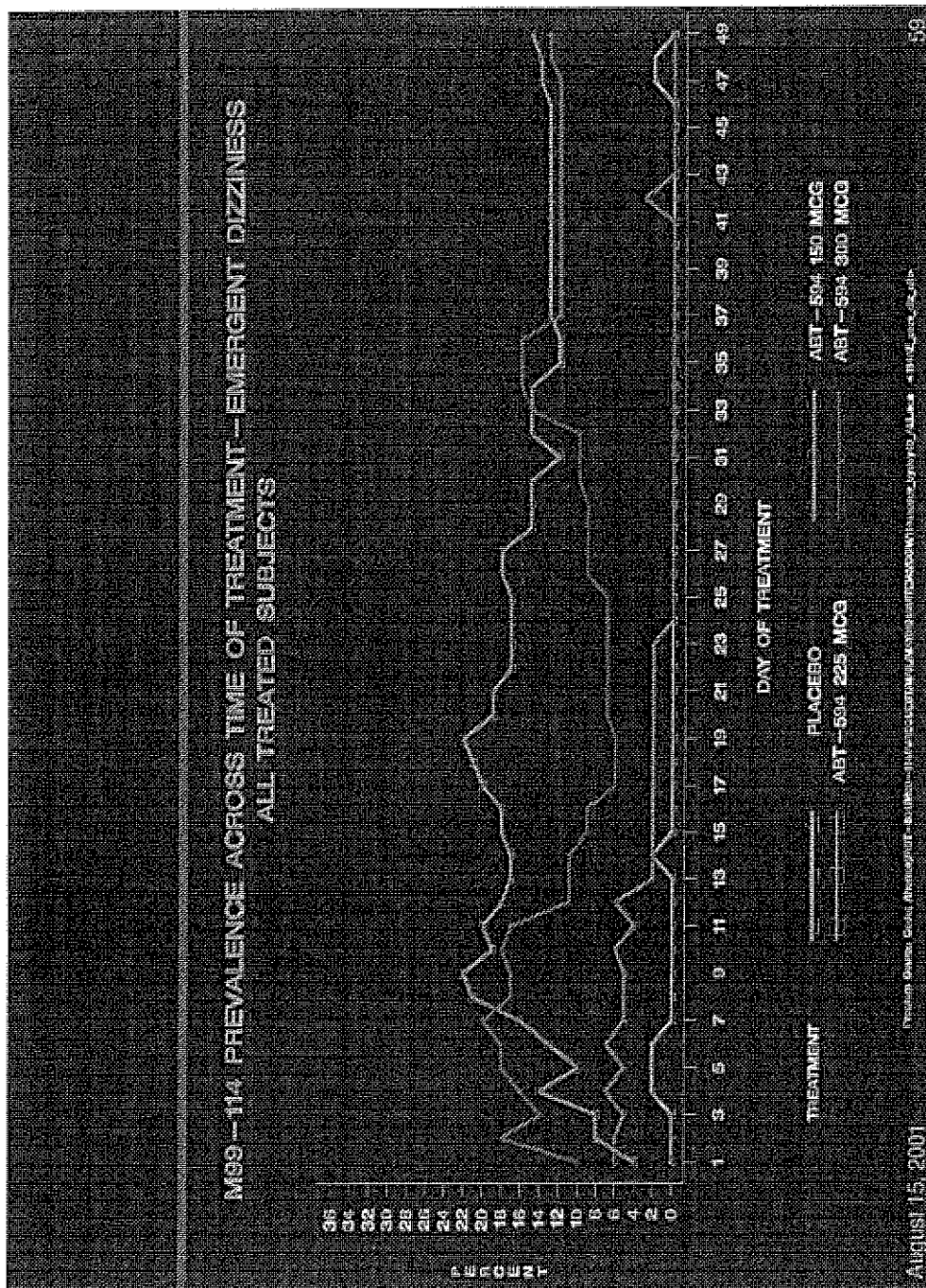
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**Confidential**

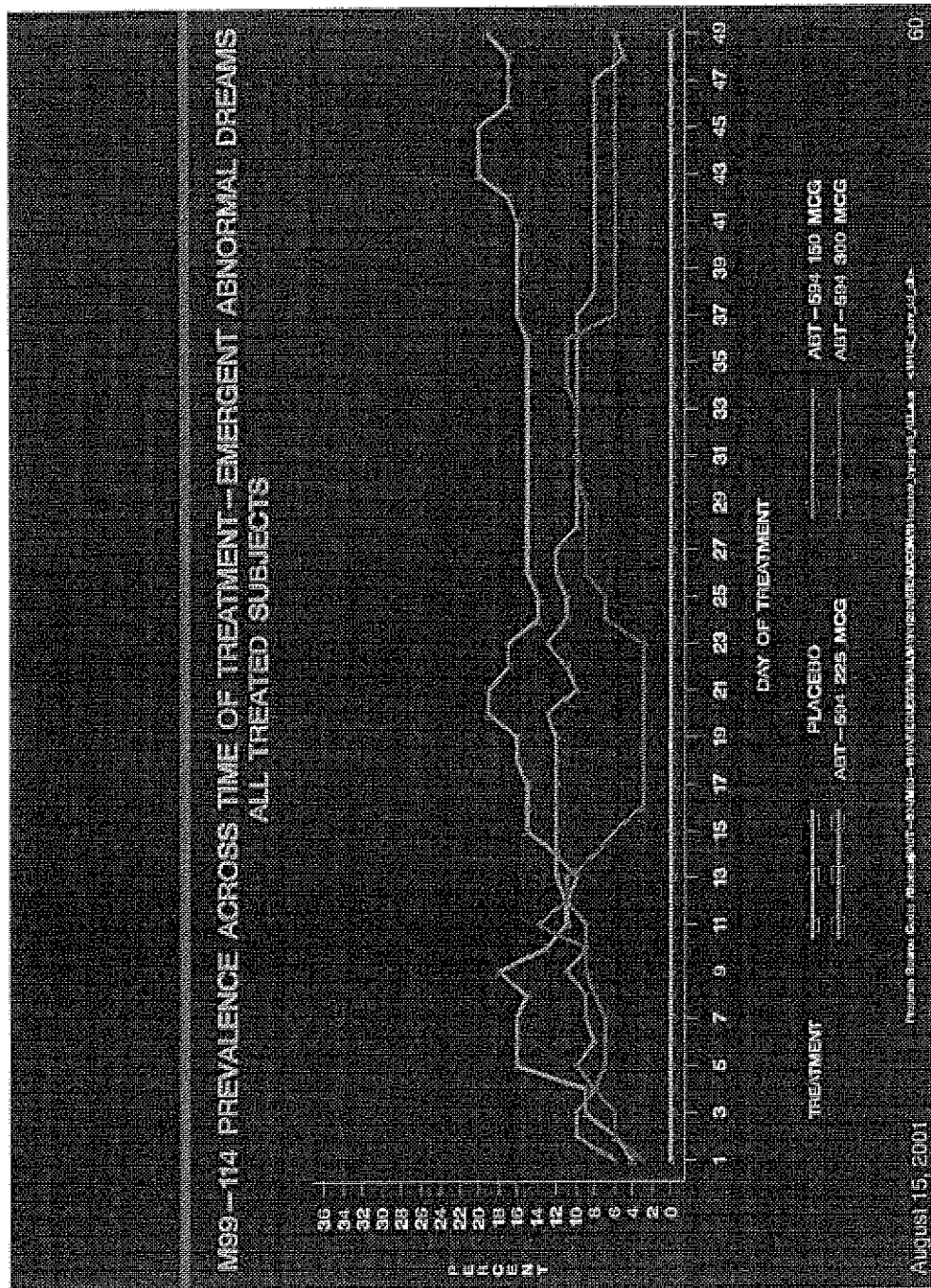
A88T311576





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ABBT311577



ABBT311578

Confidential



## Completers vs. Preterms: initial analysis

- Significant Differences
  - Gender
    - Males were more likely to complete at 150 mcg (80% vs. 20% for males, 42% vs. 58% for females)
    - More females than males preterm due to adverse events (55% vs. 39%) when all ABT-594 groups were combined
  - Baseline Pain
    - Preterms had lower baseline pain than completers at 225 mcg BID (6.3 vs. 7.3, PRS diary)
  - Weight & Height
    - Preterms had lower weight & height than completers when ABT-594 groups were combined (196 vs. 207 lbs)
  - Nicotine Use
    - Fewer users and ex-users prematurely terminated than never users when at ABT-594 groups were combined (39% vs. 53%)
- No differences
  - Gender (225, 300)
  - Race
  - Age
  - Baseline Pain (150, 300)

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**Completers vs. Preterms: Adverse Events*****150 mcg BID*****ABT-594****150 mcg BID****Completer  
(N=40)      Preterm  
(N=25)**

Diarrhea	3 (8%)	4 (16%)
Nausea	10 (25%)	12 (48%)
Vomiting*	3 (8%)	7 (28%)
Abnormal Dreams	6 (15%)	8 (32%)
Dizziness*	3 (8%)	8 (32%)

Adverse events > 10% more common in preterm  
\*p < 0.05

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ABBT311580



**Completers vs. Preterms: Adverse Events****225 mcg BID**

ABT-594  
225 mcg BID

	Completer (N=30)	Preterm (N=39)
Headache	3 (10%)	7 (18%)
Nausea	9 (30%)	21 (54%)
Vomiting*	3 (10%)	14 (36%)
Dizziness	9 (30%)	15 (38%)
Insomnia	2 (7%)	7 (18%)
Nervousness	0	4 (10%)

Adverse events > 10%, more common in preterm  
\*p < 0.05

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ABT311581

**Completers vs. Preterms: Adverse Events****300 mcg BID****ABT-594  
300 mcg BID**

	Completer (N=17)	Preterm (N=50)
Asthenia	2 (12%)	11 (22%)
Vomiting	1 (6%)	13 (26%)
Abnormal Dreams	1 (6%)	11 (22%)
Insomnia	1 (6%)	6 (12%)
Nausea	8 (47%)	23 (46%)
Dizziness	6 (35%)	13 (26%)

Adverse events > 10%, more common in preterm.

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ABT311582



## Completers vs. Preterms: Adverse Events

### All ABT-594 Subjects

ABT-594 All Subjects	
	Completer (N=87)
	Preterm (N=114)
Nausea*	27 (31%)
Vomiting*	7 (8%)
Abnormal Dreams	14 (16%)
Dizziness	18 (21%)
Insomnia	3 (3%)
	56 (49%)
	34 (30%)
	27 (24%)
	36 (32%)
	14 (12%)

Adverse events > 10%, more common in preterm  
\*p < 0.05

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ABBT311583

## Premature Termination Benchmarks

- Gabapentin in Diabetic Neuropathy
  - GBP: 17% Total, 8% AE
  - PCB: 20% Total, 6 % AE
- Pregabalin in Diabetic Neuropathy
  - PGB:
- Tramadol in Diabetic Neuropathy

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ABBT311584



## Neuropathic Pain Reminder

### Treatment Adverse Events Rates

Event      Amitriptyline  
150 mg/d<sup>1</sup>      Carbamazepine  
600 mg/d      Gabapentin  
3600 mg/d      Pregabalin  
300 mg/d

Confusion	N/A	N/A	8%	5%
Somnolence	56%	53%	23%	24%
Dizziness	28%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

<sup>1</sup> Max: 1987 (n=29)  
N/A - Not Available

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ABBT311585

ABT-594 150, 225 and 300 mcg BID Were Associated with a Dose Dependent Increase in Adverse Events, Especially Nausea, Vomiting and Dizziness: All Subjects

### *Adverse Events*

Event	ABT-594 150 mcg BID		ABT-594 225 mcg BID		ABT-594 300 mcg BID	
	Placebo N = 65	N = 65	Placebo N = 69	N = 69	Placebo N = 67	N = 67
Nausea	11 %	34 %*	43 %*	46 %*		
Abnormal Dreams	0 %	22 %*	22 %*	18 %*		
Headache	12 %	20 %	14 %	19 %		
Dizziness	5 %	17 %*	35 %*	28 %*		
Vomiting	3 %	15 %*	25 %*	21 %*		
Diarrhea	3 %	11 %	12 %	6 %		
Dyspepsia	3 %	8 %	12 %	7 %		
Asthenia	2 %	6 %	16 %*	19 %*		

Occurring in ≥5% 150 mcg BID ABT-594 treated patients and ABT-594 incidence > placebo  
\*p<0.05 vs. placebo

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ABT311586



95% Confidence Intervals for Nausea, Vomiting and Dizziness

*Adverse Events*

	150 mcg BID	225 mcg BID	300 mcg BID
Nausea	34% [22, 45]	43% [32, 55]	46% [34, 58]
Vomiting	15% [7, 24]	25% [14, 35]	21% [11, 31]
Dizziness	17% [8, 26]	35% [24, 46]	30% [19, 41]

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ABB1311587

# Increasing Levels of Pain Reduction May Trend with Increasing Incidence of Adverse Events at 300 mcg BID

## 300 mcg BID (ITT) Pain Reduction Quartiles

	Least Pain Reduction n=12	Quartile n=10	Quartile n=16	Most Pain Reduction n=15
Nausea	42%	40%	50%	60%
Vomiting	17%	20%	25%	27%
Dizziness	42%	0%	38%	20%

August 15, 2001

70

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ABBT311588

# Meyer Deposition Exhibit 23

## D's Exhibit 661 – Part 5



**Sample Size Is Too Small to Make Conclusions About  
The Relationship Between Level of Pain Reduction and  
Treatment Emergent Adverse Events for Completers**

**300 mcg BID (Completers)  
Quartile Pain Reduction**

	Least Pain Reduction n=2		Quartile n=1		Quartile n=6		Most Pain Reduction n=8	
Nausea	0%	0%	0%	0%	50%	50%	63%	63%
Vomiting	0%	0%	100%	100%	0%	0%	0%	0%
Dizziness	0%	0%	0%	0%	50%	50%	38%	38%

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ABBT311589



## QT Assessment

- M99-114 not designed to assess QT
- Mean QT
- Individual QTc (Bazett) Changes (on drug)
  - #4081: From 441 ms to 520 ms
    - Abt (BGM) re-read *would* be from 521 to 439 ms
- Syncope
  - #4083: h/o afib, to ER for “syncope”, refuses to release medical records

August 15, 2001

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ABT311590

## ABT-594

### *Questions*

- Where do doses evaluated to date fit on the dose-response curve?
  - PK/PD Effect
- Can tolerability be improved?
  - Differentiation of patient populations
  - Dosage administration
- If tolerability is improved, will there be even more efficacy?
- How much will patients benefit from ABT-594?
  - If administered as in M99-114
  - Given hypothetical improvements in tolerability & efficacy

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ABT311591



## ABT-594 IS A MAJOR SCIENTIFIC ACHIEVEMENT

- *Independent of future business decisions regarding ABT-594...*

- ABT-594 is the first drug ever to be successfully discovered and developed with the intent purpose to treat neuropathic pain (and other pain disorders).
- NNRS are now fully validated as a viable mechanism to treat neuropathic pain
- For the first time in decades there is now an additional class of analgesic agents:

- **NNRS**
- OPIOIDS
- NSAIDs/COX-2s
- ACETAMINOPHEN
- TCAs/AEDs

August 15, 2001

74

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ABT311592

# ABT-594

## *Pharmacokinetics and Metabolism*

- Half-life ( $t_{1/2}$ ): about 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{max}$  similar with/without food
- $T_{max}$  varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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75

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ABBT311593



## Molar Extraction Study

### Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo
Single dose	

- Third molar extraction
- Outcome measures:  
Pain relief (PR)

Categorical scale:

0 1 2 3 4  
none a little some a lot complete

- Power: 70% to detect an effect similar to acetaminophen plus codeine
- Solution

August 15, 2001

76

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ABBT311594

# Molar Extraction Study

## Outcome Measures

- **Pain Relief (PR)**
  - Categorical scale: 0 none 1 a little 2 some 3 a lot 4 complete
- **Total Pain Associated Relief (TOTPAR)**
  - Area under the curve for PR (0-6 hours)
- **Pain Intensity (PI)**
  - Categorical scale: 0 none 1 mild 2 moderate 3 severe
- Visual Analog Scale
 
- **Stop Watch Model**
  - Time to "perceptible" and "meaningful" relief
- **Time To Rescue Medication**
- **Patient Global**
  - Rate medication: 1 poor 2 fair 3 good 4 excellent

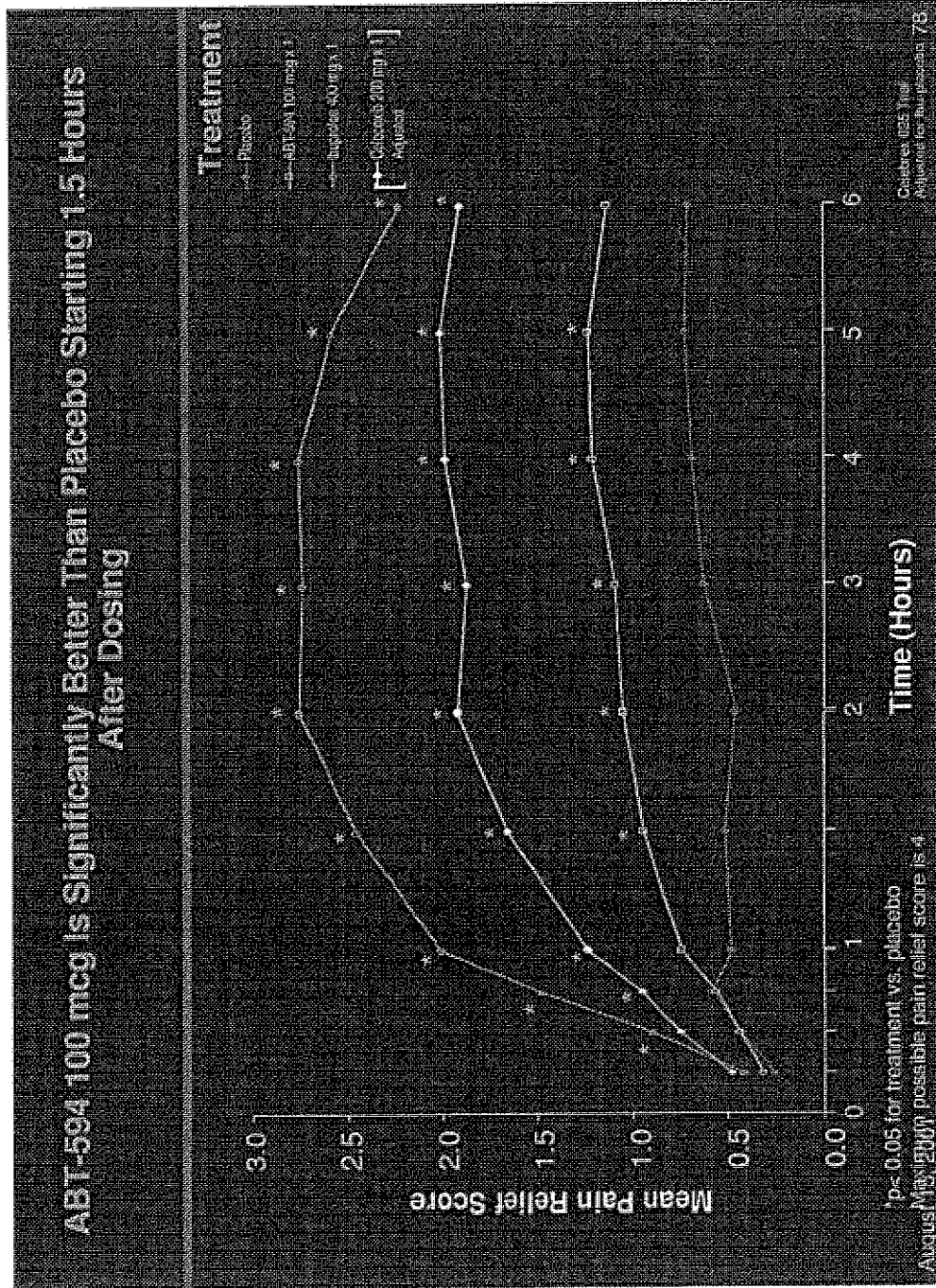
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77

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ABBT311595





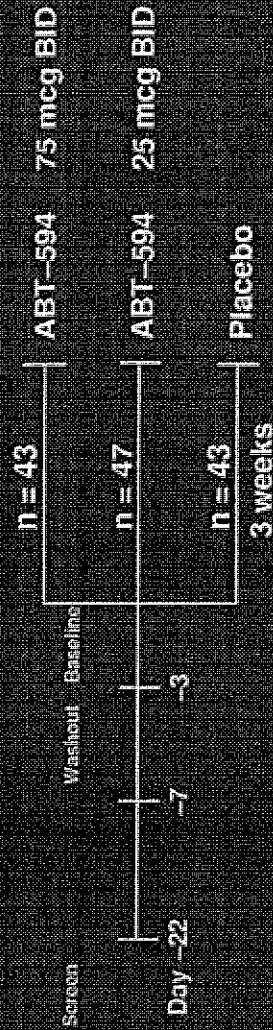
ABBT311596

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## Neuropathic Pain Pilot

### Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
  - 52% idiopathic
  - 46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

August 15, 2001

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ABT311597



# Neuropathic Pain Pilot

## Outcome Measures

- **Pain Intensity (PI)**

- Categorical Scale:



- Visual Analog Scale: (0-100 mm)

- **Neuropathic Pain Scale (NPS)**

- 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp 

1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	----

 The most **sharp** sensation imaginable ("like a knife")

- **Patient Global (PG)**

- Rate Medication:

1	2	3	4
poor	fair	good	excellent

August 15, 2001

80

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ABB1311598

# **ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared to Placebo in Neuropathic Pain**

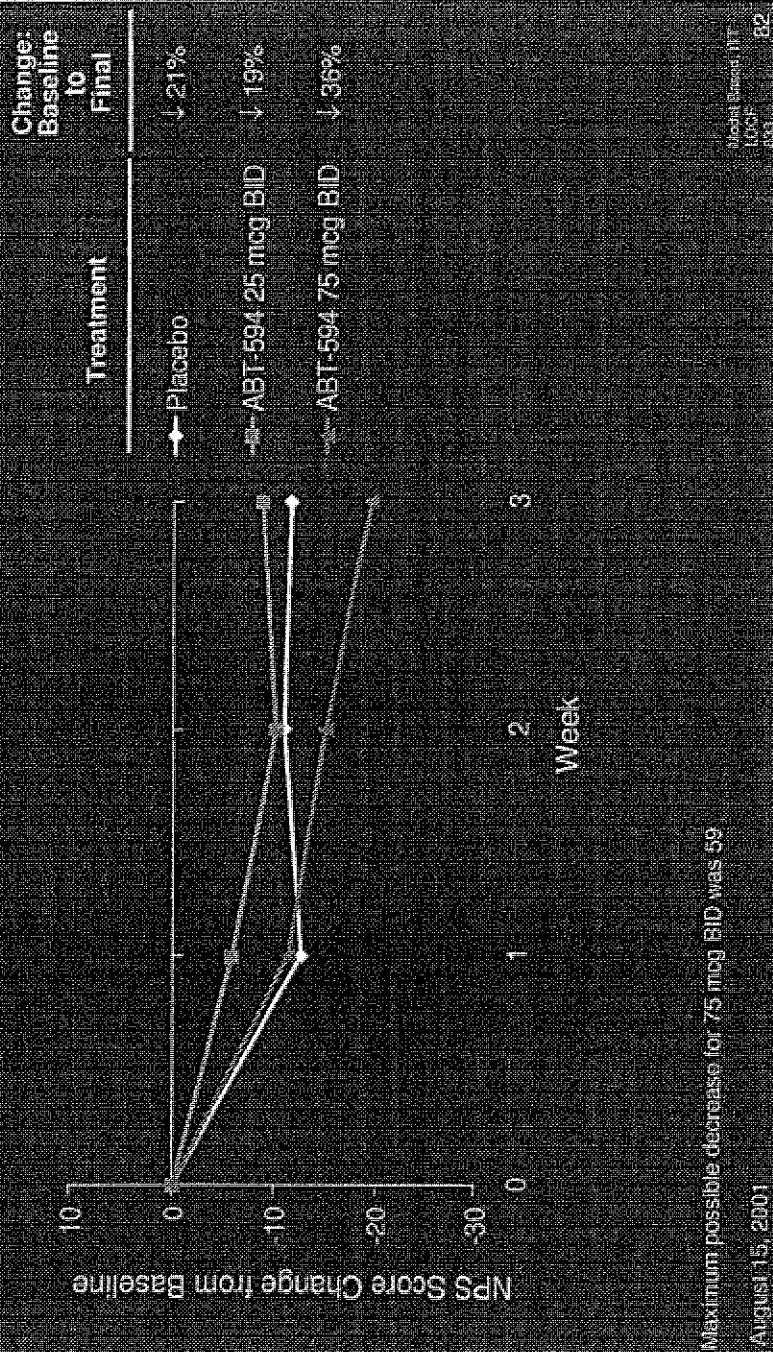


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ABT311599

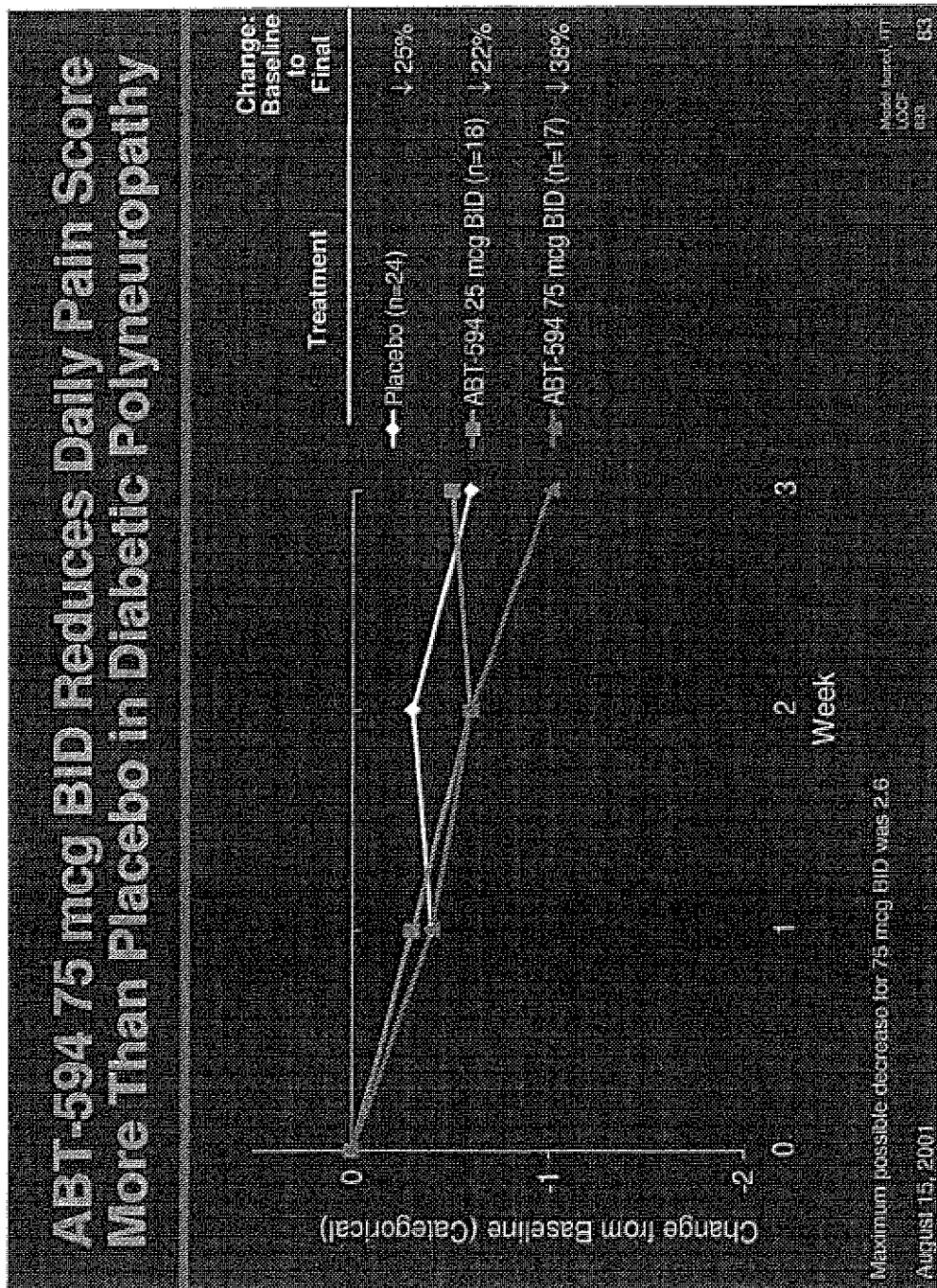


# **ABT-594 75 mcg BID Reduces the NPS More Than Placebo**



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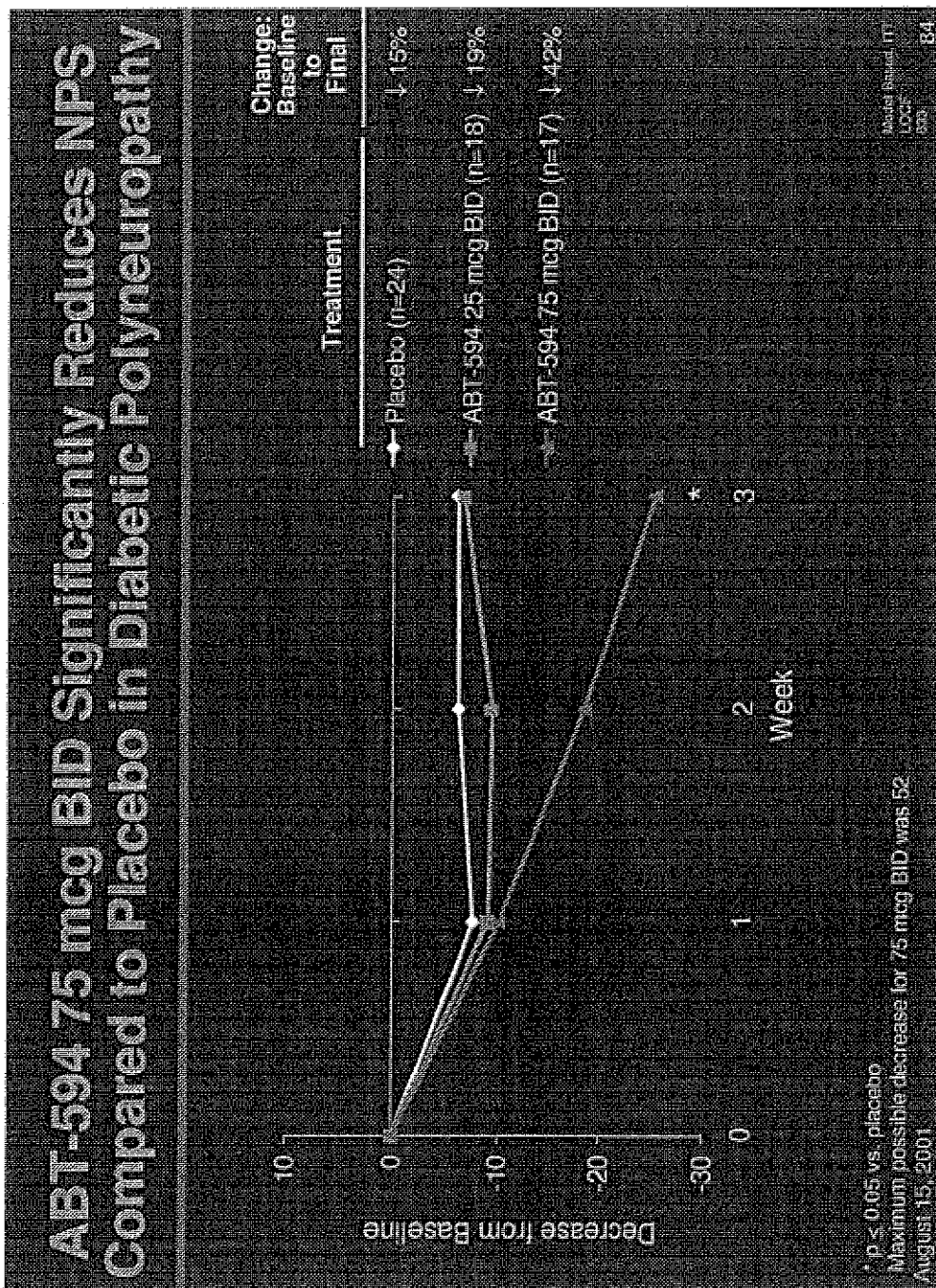
ABBT311600



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ABBT311601



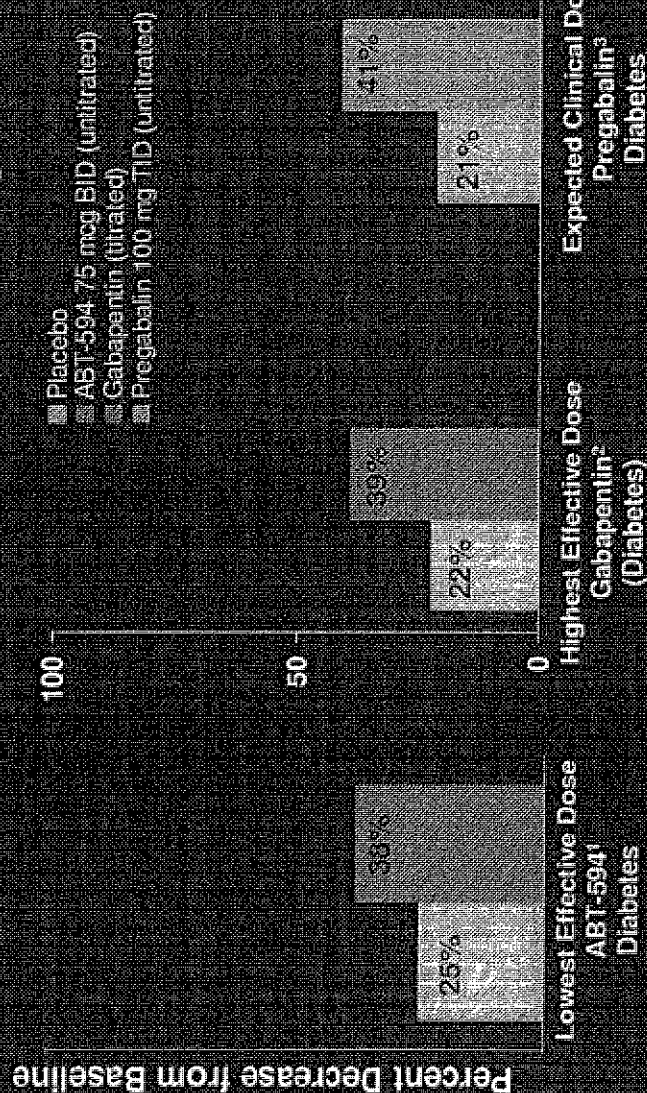


Confidential

ABT311602

# **ABT-594 75 mcg BID has a Similar Effect To Gabapentin**

## *ABT-594 vs. Gabapentin and Pregabalin*



<sup>1</sup> 4-point categorical scale final vs. baseline  
<sup>2</sup> 11-point Likert Scale week 8 vs. baseline  
<sup>3</sup> 11-point Likert scale week 5 vs. baseline

August 15, 2001

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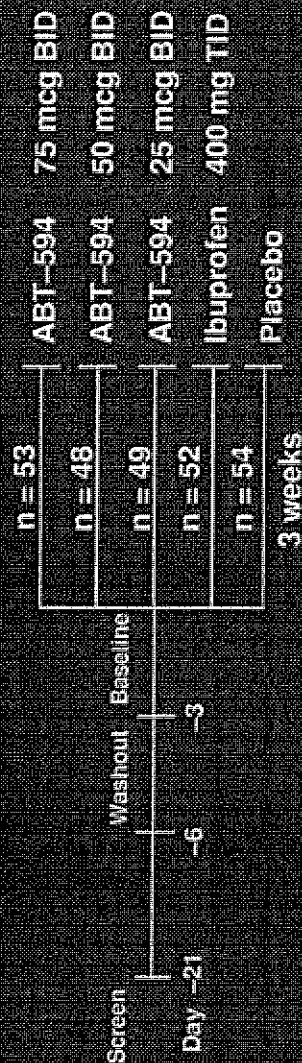
ABB311603



# Osteoarthritis Pain Pilot

## Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

August 15, 2001

86

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ABT311604

# Osteoarthritis Pain Pilot Study

## Outcome Measures

- **Pain Intensity (PI)**

- Categorical Scale:

0	1	2	3
none	mild	moderate	severe

- Visual Analog Scale (VAS):



- **WOMAC**

- Pain (0-500)
  - Stiffness (0-200)
  - Function (0-1700)

Total (0-2400)

- **Patient Global**

- Rate Medication:

1	2	3	4
poor	fair	good	excellent

August 15, 2004

87

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ABBT311605



**Osteoarthritis Pain Pilot Study**

---

**WOMAC**

**Pain**      How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain | extreme pain

**Stiffness**      How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness | extreme stiffness

**Function**      What degree of difficulty do you have...

- Descending stairs?
- Rising from bed?

no difficulty | extreme difficulty

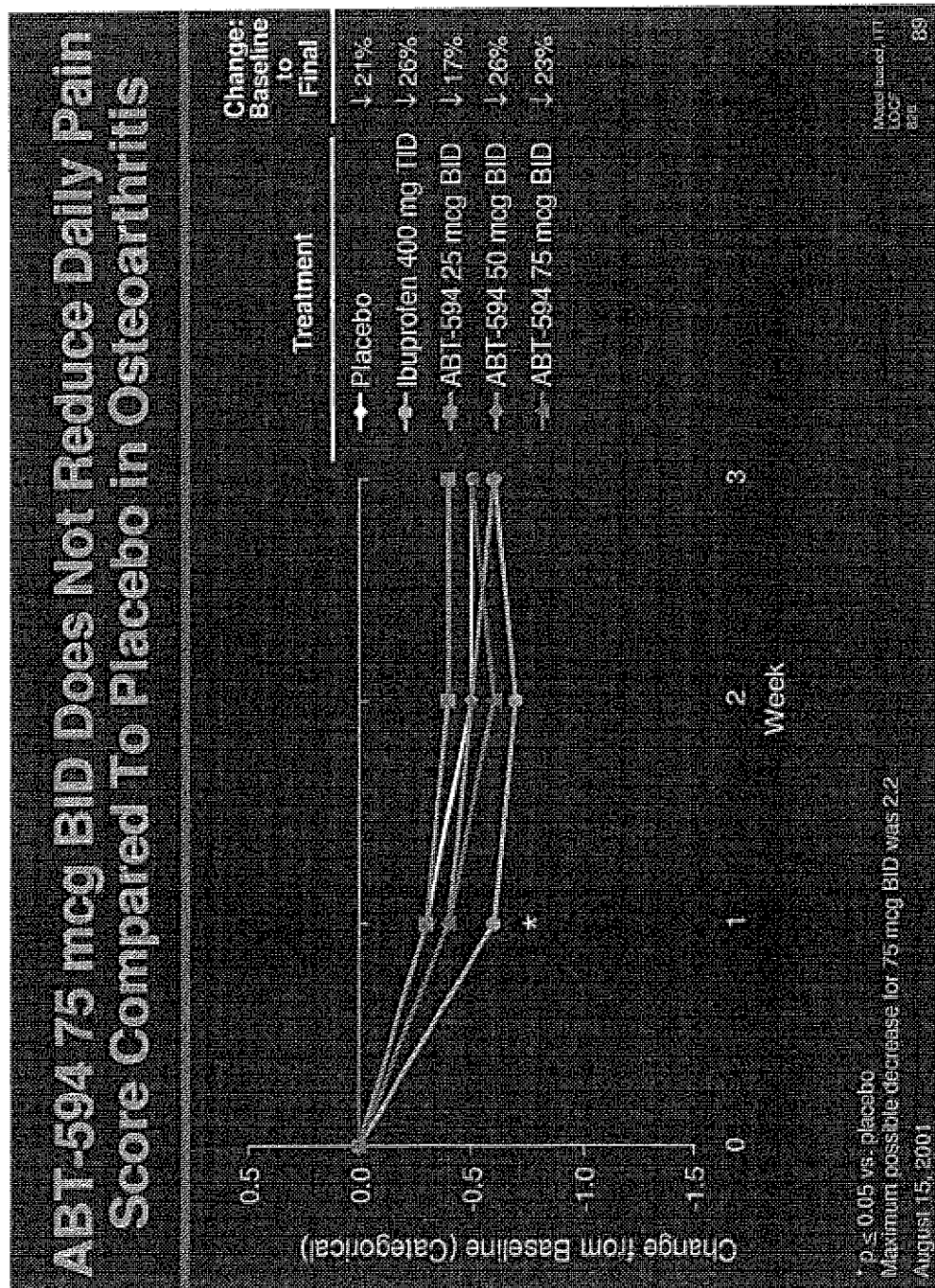
August 15, 2001

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ABBT311606

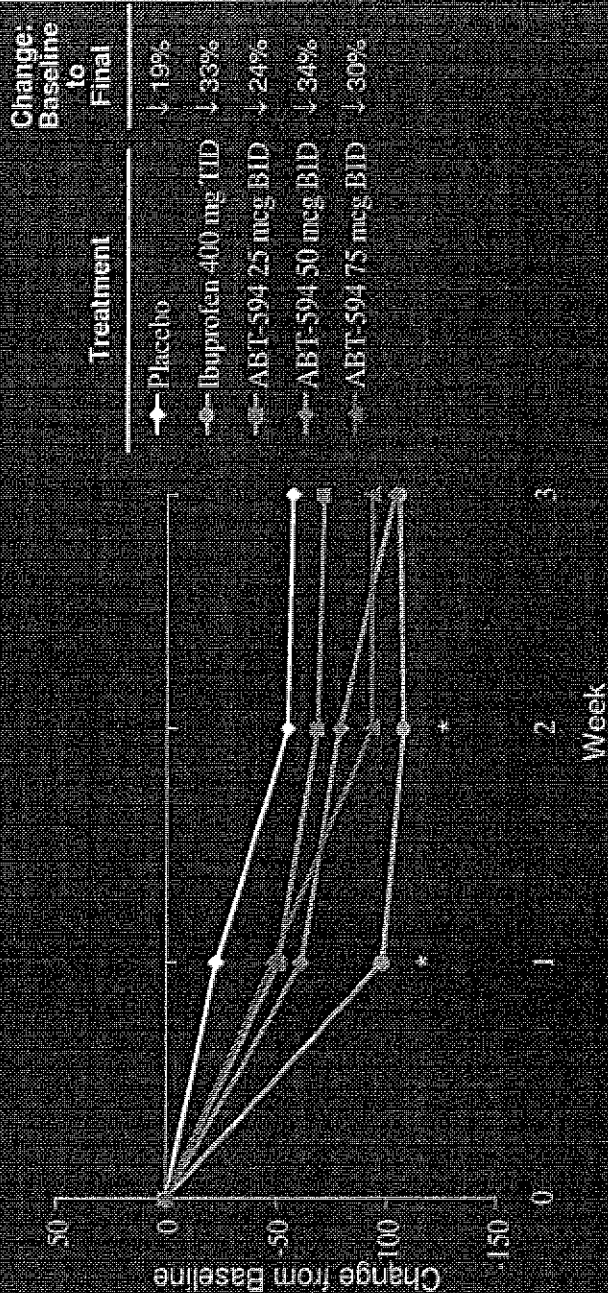




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ABT311607

# ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis



\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 305

Based on 5-item (0-500 points)

August 15, 2001

90

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ABBT311608

# Meyer Deposition Exhibit 23

## D's Exhibit 661 – Part 6



# **ABT-594 75 mcg BID Has An Effect Similar to Celebrex**

*WOMAC Pain Decrease from Baseline*



August 15, 2001

91

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ABBT311609

## Gabapentin Study

### Design

- 162 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- Power (planned): 75 patients/group, > 80% power to detect 25% difference (gabapentin vs. placebo)
- Entry: average  $\geq 4$  on 11-point Likert on at least 4 observations during baseline week; no concomitant analgesics

Backonja et al., 1998

August 15, 2001

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ABB311610



## Gabapentin Study

---

### Outcome Measures

- **Primary**
  - 11-point Likert (0=no pain; 10=worst pain)
- **Secondary**
  - SFMPQ VAS
 

no pain

worst possible pain
  - SFMPQ PPI
 

0 no pain
1 Mild
2 Discomforting
3 Distressing
4 Horrible
5 Excruciating

– Patient global impression of change (7 point scale)

August 15, 2001
Backonja et al. 1998

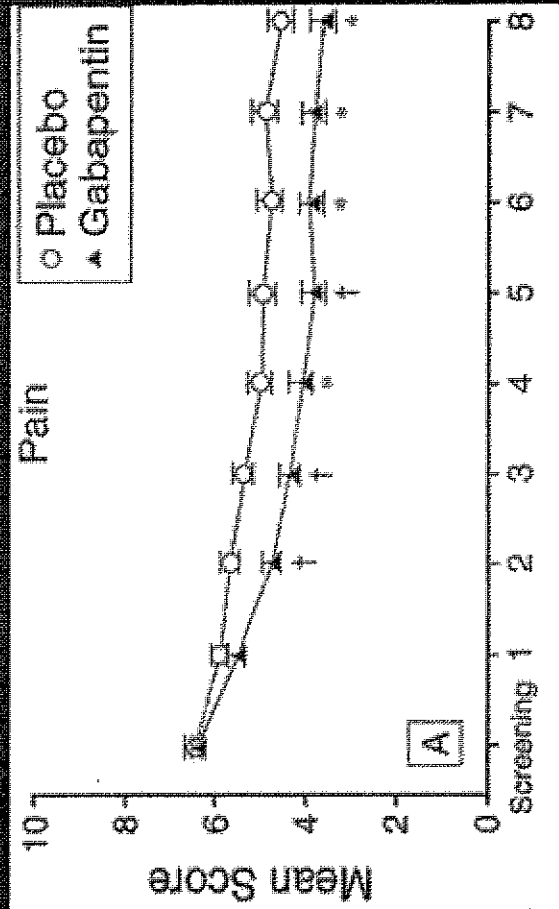
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# Gabapentin Study

## Results

### • Primary



Backonja et al, 1998

August 15, 2001

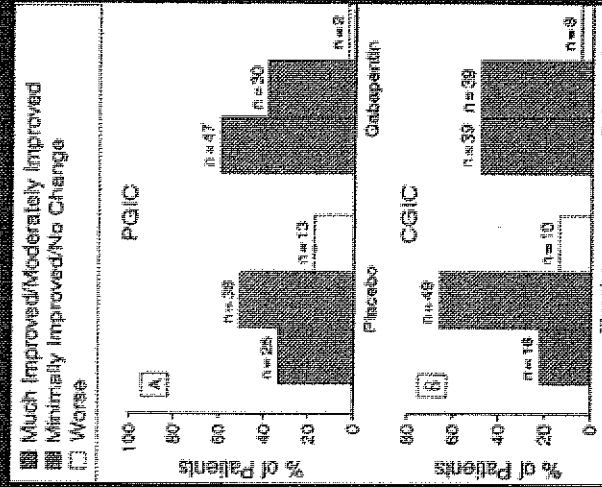
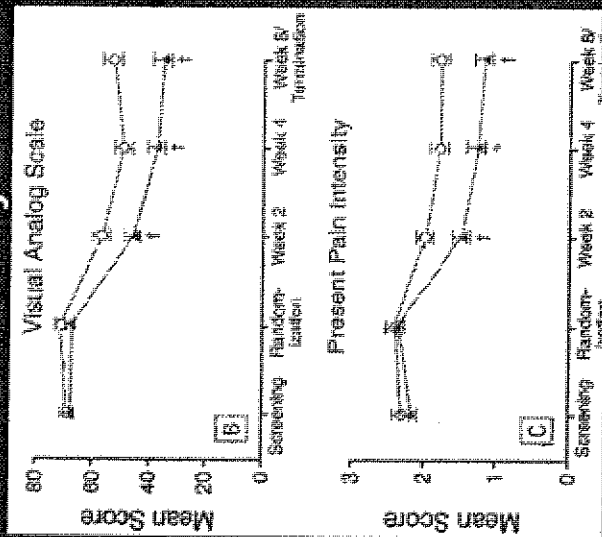
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A88T311612

# Gabapentin Study

## Results

### Secondary



August 15, 2001 Backonja et al. 1998

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ABBT311613



## Gabapentin Studies

### Adverse Events

#### Adverse Event Rate (%)

	Gabapentin	(placebo)
Dizziness	20	(4)
Somnolence	19	(5)
Headache	9	(3)
Diarrhea	9	(7)
Confusion	7	(1)
Nausea	7	(4)

August 15, 2001

Bachman et al, 1998

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ABBT311614

## Pregabalin Studies

### Design - 014

- 246 patients, randomized, double-blind, placebo-controlled



- Power not specified
- Entry
  - Average  $\geq 4$  on 11-point daily Likert during baseline
- Discontinuation due to adverse events:
 

600 mg/d	8.5%
150 mg/d	2.5%
Placebo	4.7%

Sharma et al. 2000

August 15, 2001

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ABB311615



## Pregabalin Studies

### *Outcome Measures - 014*

- Primary
  - Weekly mean Likert pain score (probably)
- Secondary
  - Responder rate
  - Patient global impression of change
  - Sleep interference score
  - SFMPQ

Sharma et al, 2008

August 15, 2001

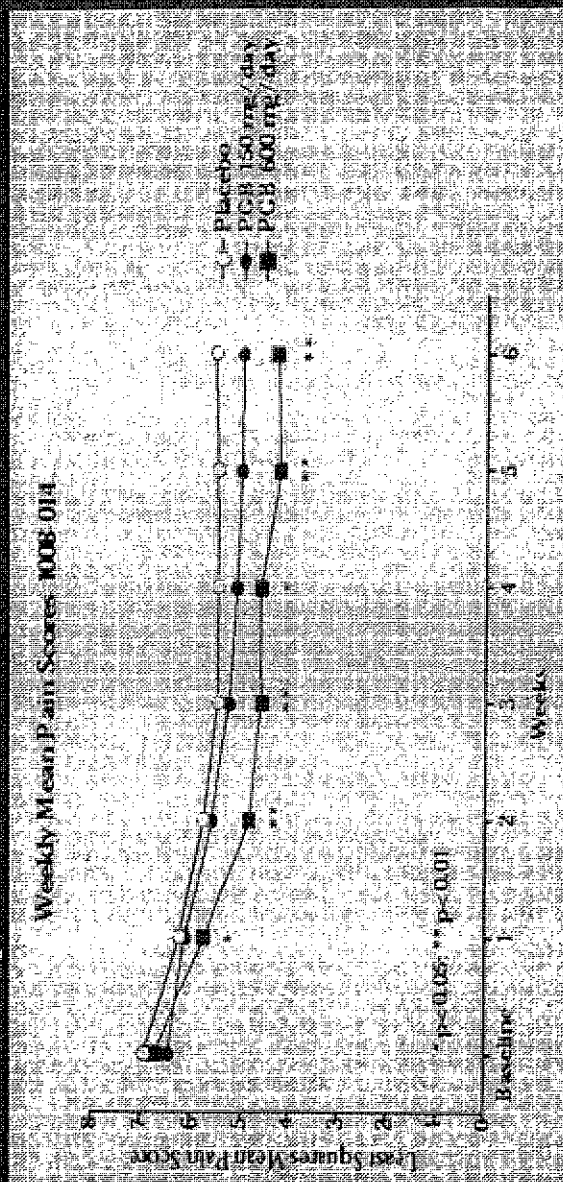
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# Pregabalin Studies

## Results - 014

### • Primary



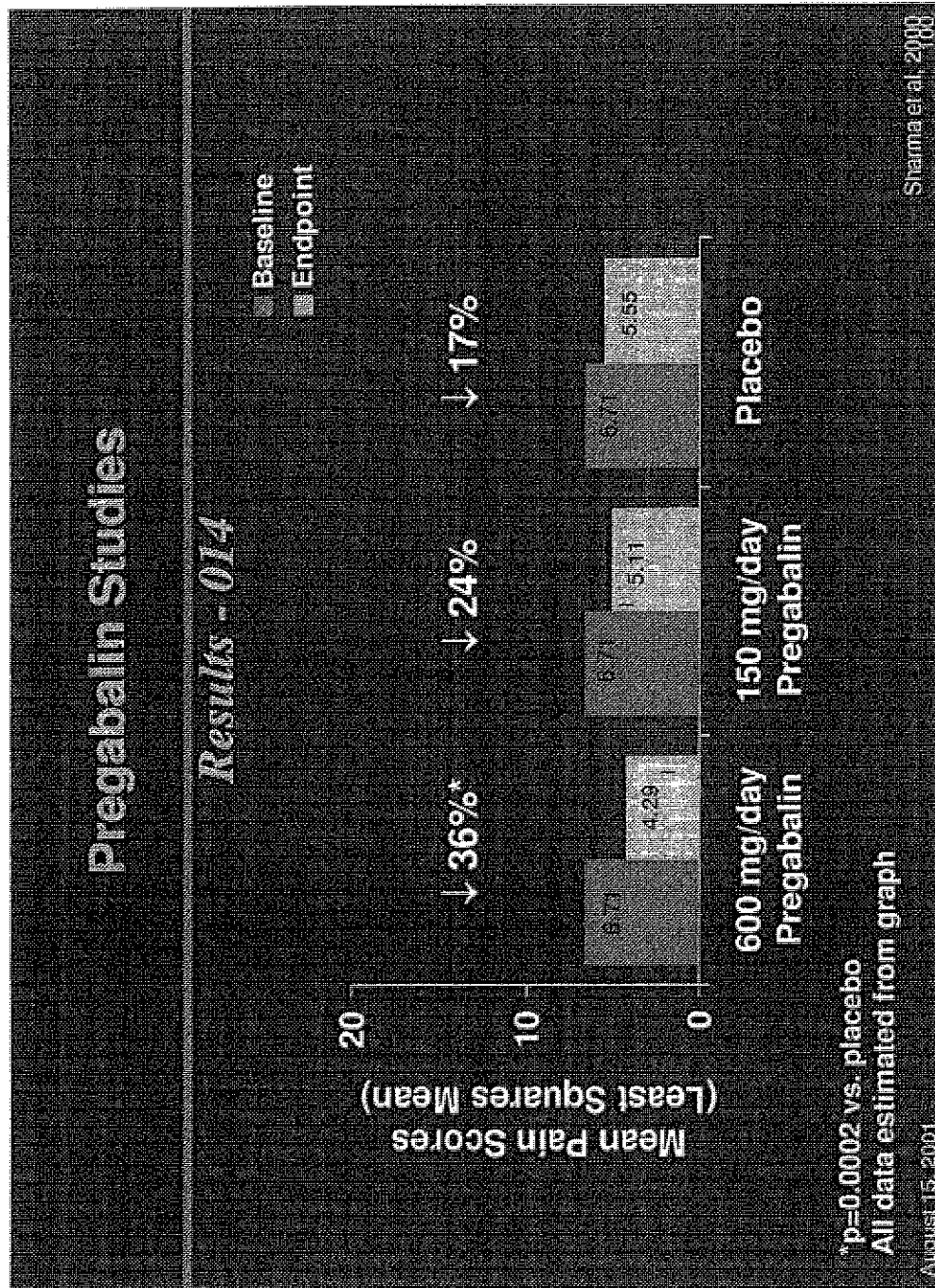
Sharma et al, 2000

August 15, 2001

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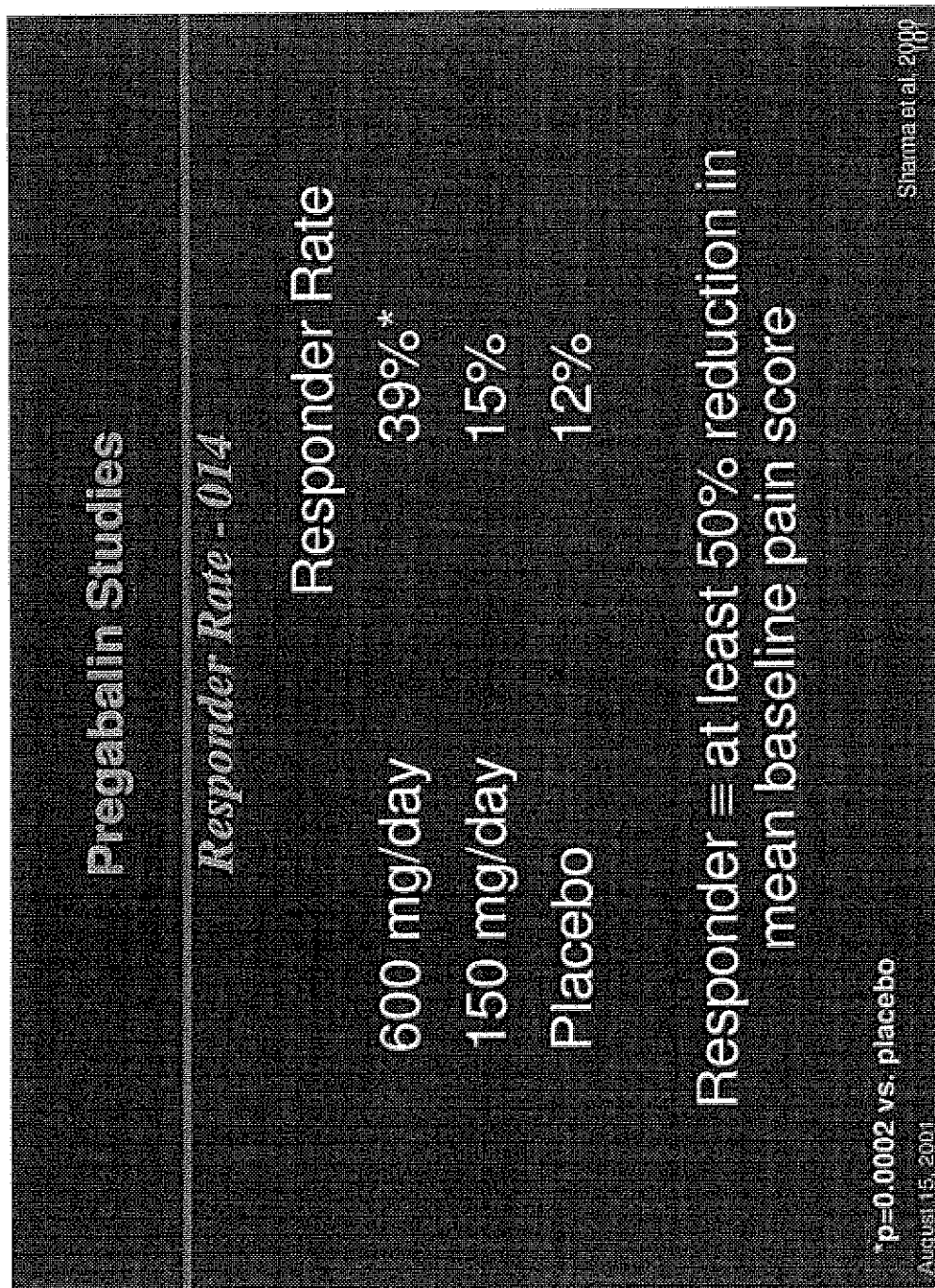
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ABBT311618



ABBT311619

Confidential



## Pregabalin Studies

### Adverse Events - 014

	600 mg/d (%)	150 mg/d (%)	Placebo (%)
Dizziness	37.8	10.1	2.4
Somnolence	22.0	5.1	3.5
Peripheral edema	17.1	3.8	4.7
Asthenia	12.2	3.8	3.5
Weight gain	9.8	2.5	0.0
Amblyopia	8.5	2.5	5.9
Dry mouth	8.5	0.0	2.4

Headache and accidental injury not included

August 15, 2001

Sharma et al, 2003

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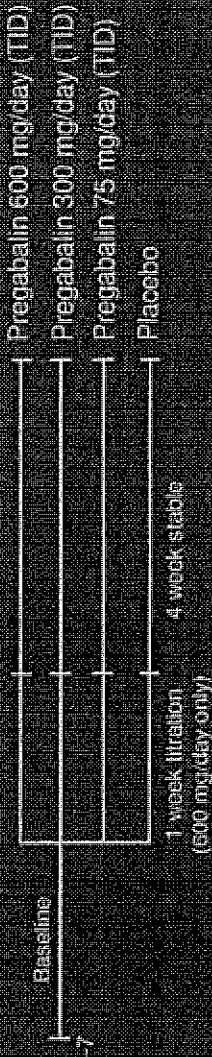
ABBT311620



## Pregabalin Studies

### Design - 029

- 338 patients, randomized, double-blind, placebo-controlled



- Power not specified
- Entry
  - Average  $\geq 4$  on 11-point daily Likert during baseline
- Discontinuation due to adverse events:
 

600 mg/d	12.2%
300 mg/d	3.7%
75 mg/d	2.6%
Placebo	3.1%

Sharma et al. 2003

August 15, 2001

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ABBT311621

## Pregabalin Studies

### *Outcome Measures - 029*

- Primary
  - Weekly mean Likert pain score (probably)
- Secondary
  - Responder rate
  - Patient global impression of change
  - Sleep interference score
  - SFMPQ

August 15, 2001

Sharma et al. 2009

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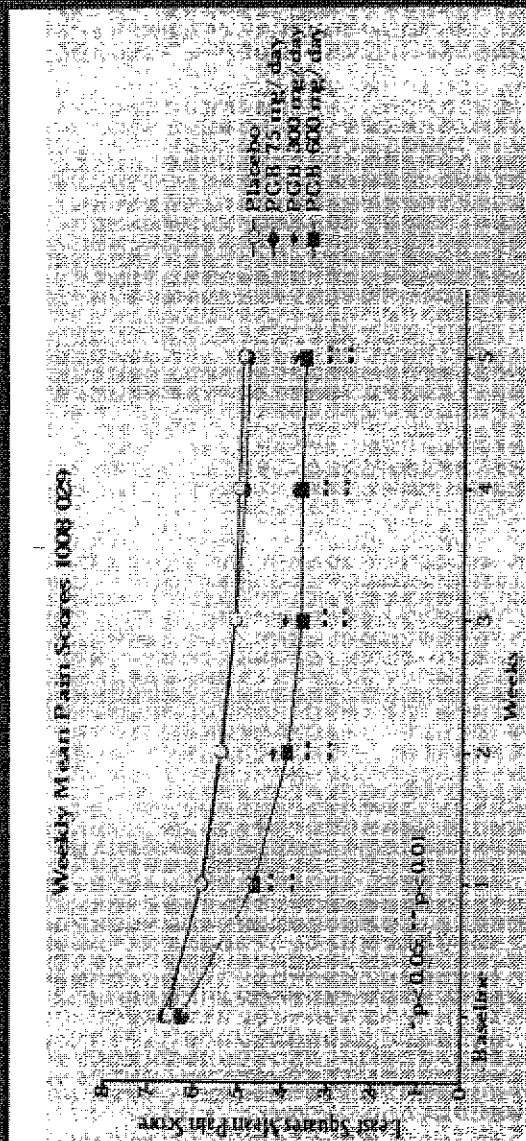
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# Pregabalin Studies

## Results - 029

### • Primary

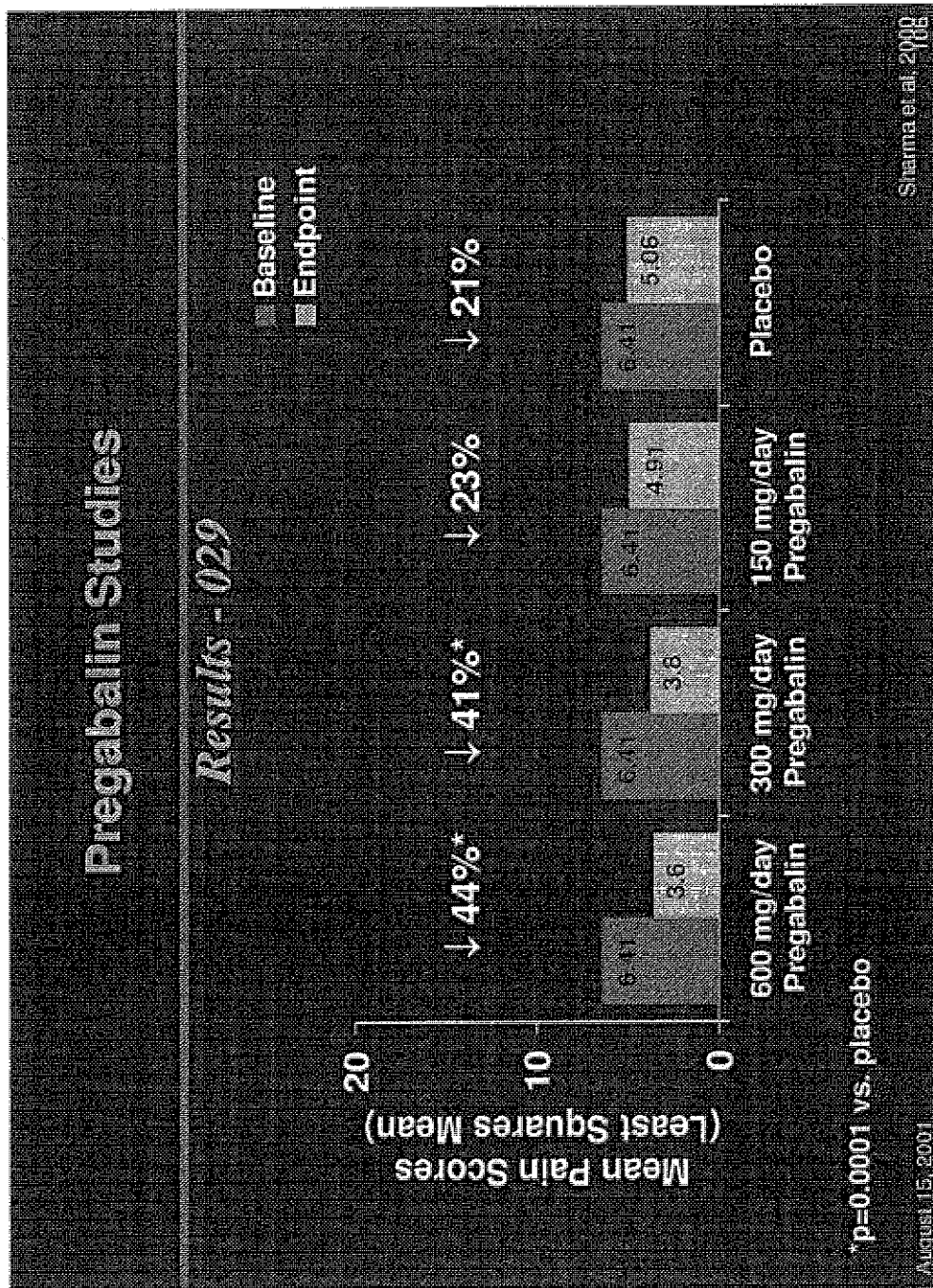


Sharma et al. 2000

August 15, 2001

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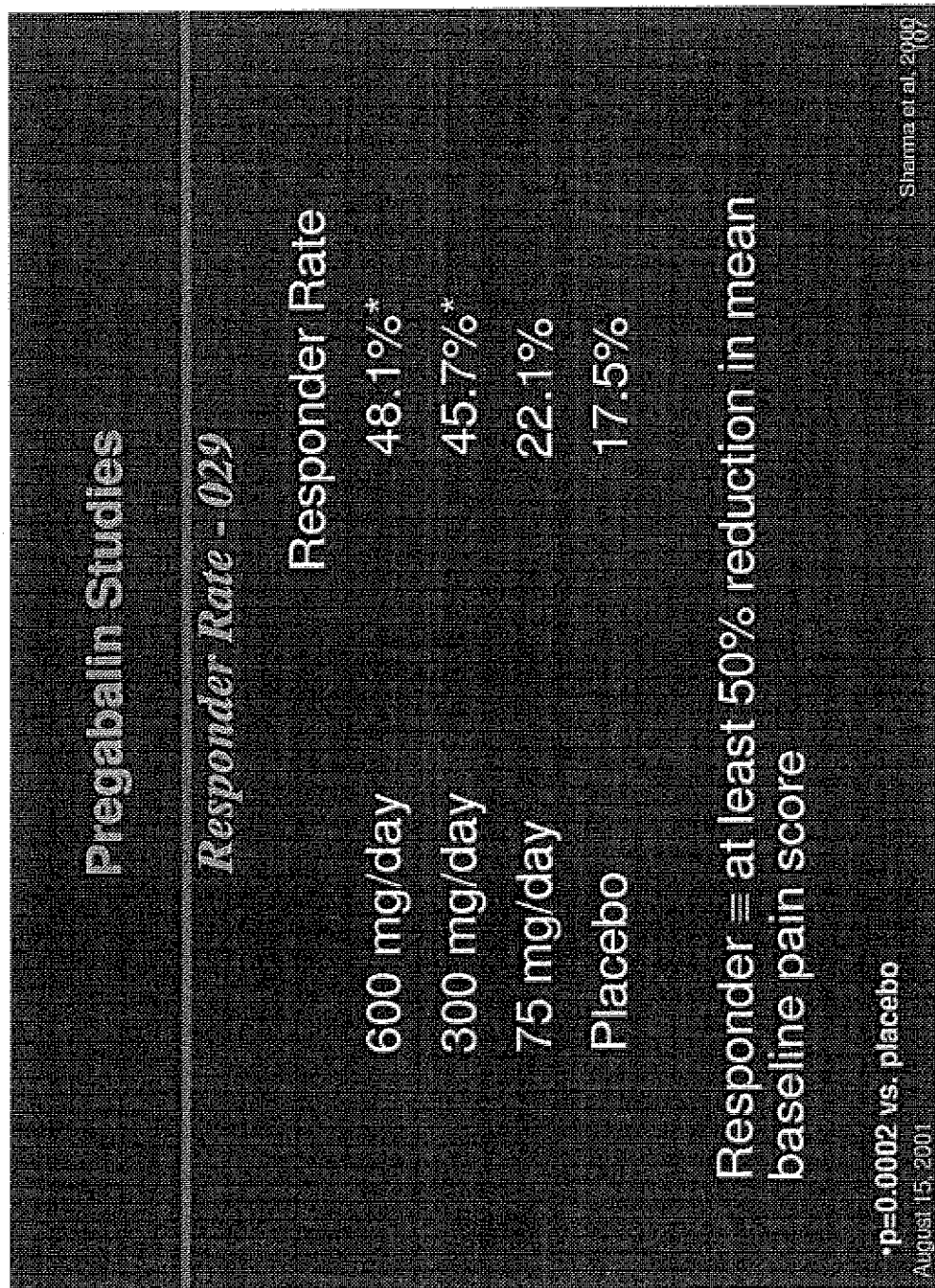
ABBT311623



ABBT311624

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ABBT311625



## Pregabalin Studies

### Adverse Events - 029

	600 mg/d (%)	300 mg/d (%)	75 mg/d (%)	Placebo (%)
Dizziness	39.0	27.2	7.8	5.2
Somnolence	26.8	23.5	3.9	4.1
Peripheral edema	13.4	7.4	3.9	2.1
Amblyopia	8.5	4.9	2.6	1.0
Ataxia	8.5	3.7	6.5	2.1
Confusion	8.5	4.9	0.0	2.1
Constipation	8.5	3.7	0.0	0.0

Headache not included

August 15, 2001

Sharma et al, 2008

Confidential

ABB311626

## Pregabalin Studies

### *Responder Rate - 131*

#### Responder Rate

300 mg/day 40.0 %\*

Placebo 14.5 %

Responder = at least 50% reduction in  
mean baseline pain score

•  $p=0.001$  vs. placebo  
August 15, 2001

Sharma et al. 2003  
109

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ABBT311627

## Meyer Deposition Exhibit 23

D's Exhibit 661 – Part 7



## Tramadol Study

### Design

- 131 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- Power: 85% to detect a difference of 0.8 (on 5-point scale, tramadol vs. placebo)
- Moderate (2) or greater; no concomitant analgesics

August 15, 2001

Marati et al, 1998  
110

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ABB311628

## Tramadol Study

### Outcome Measures

- Primary

- 5 point Likert pain intensity (at visits)

0 none  
1 mild  
2 moderate  
3 severe  
4 extreme

- Secondary

- Patient rated pain relief score

Complete 4  
A lot 3  
Moderate 2  
Slight 1  
None 0  
Worse (-1)

- Medical Outcome Study measures of daily living activities and sleep

Marati et al. 1998

August 15, 2001

Confidential

ABBT311629



# Tramadol Study

## Results: Primary



\*  $p \leq 0.001$  vs. placebo  
 Maximum possible decrease for tramadol was 2.5  
 Some data estimated from graphical presentation

August 15, 2001

Marati et al. 1998  
 1/2

Confidential

ABBT311630

## Tramadol Study

### Adverse Events

#### Adverse Event Rate (%)

#### Tramadol (placebo)

Nausea	23	(3)
Constipation	22	(3)
Somnolence	12	(6)
Dyspepsia	9	(3)
Pruritis	6	(0)
Rash	6	(0)
Vomiting	5	(0)
Fatigue	5	(0)
Dizziness	5	(0)

Marabi et al. 1998  
113

August 15, 2001

Confidential

ABBT311631



## Topiramate Study

### Design

- 27 patients, randomized (2:1 topiramate to placebo), double-blind, placebo-controlled



- Diabetic polyneuropathy

- Not powered

- Entry

- No concomitant analgesic medications
- $\geq 40$  mm/100 mm SFMPQ-VAS at baseline visit
- $\geq 4$  on 11-point Likert pain scale at baseline visit

August 15, 2001

Edwards et al. 1999  
114

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ABST311632

## Topiramate Study

### *Outcome Measures*

- Primary
  - SFMPQ-VAS
- Secondary
  - SFMPQ-Total
  - Patient global impression of change

Edwards et al. 1999  
143

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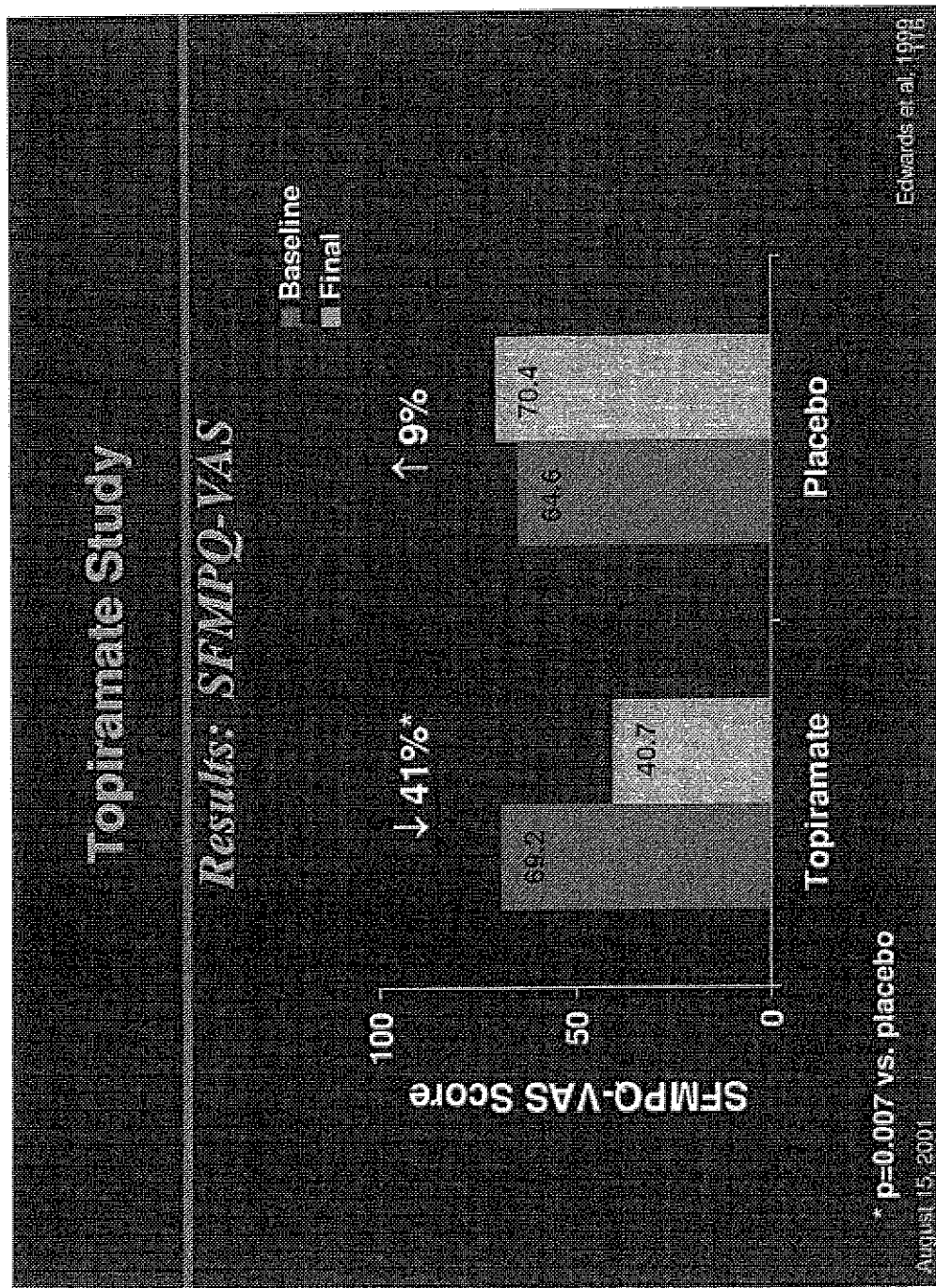
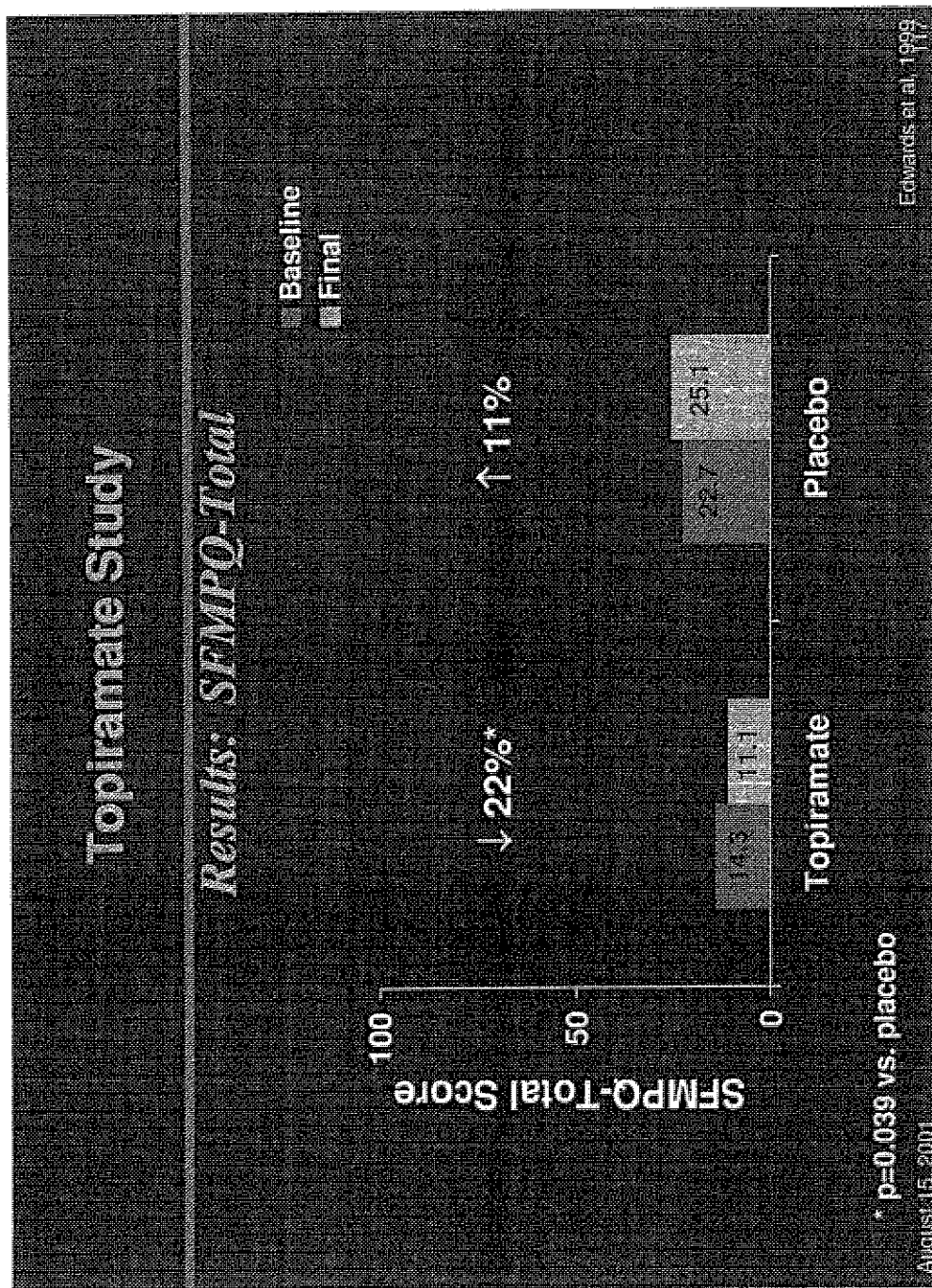


ABB7311634

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ABBT311635

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## Topiramate Study

### Adverse Events

#### Adverse Event Rate (%)

#### Topiramate (placebo)

Asthenia	56	(0)
Weight loss of > 10%	22	(0)
Confusion	22	(0)
Paresthesia	17	(0)
Lightheadedness	17	(0)
Dry mouth	17	(0)

Edwards et al, 1999  
118

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ABBT311636



## Amitriptyline for Neuropathic Pain

*Max, 1987*

- Largest (active) placebo-controlled, randomized, double-blind trial of a tricyclic
  - N=29 (completers); 5 discontinued due to AEs
  - 2-week drug-free baseline, 6-week crossover (no washout); 3-week titration, 3-week stable (150 mg)
- Primary endpoint – 13 word verbal description (numeric equivalents)
 

Placebo	↓ 14%	(estimated from graph)
Amitriptyline	↓ 51%	
- Adverse events
 

Dry mouth	90%
Sedation	66%
Dizziness	28%
Constipation	14%

August 15, 2001

119

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ABBT311637

# **Meyer Deposition Exhibit 26**

**P's Exhibit GM**



Michael D  
Meyer/LAKE/PPRD/ABBOTT

06/07/2002 12:49 PM

To Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT,  
Joseph Stautler/HPD/Abbott@Exchange@ABBOTT, Danhui  
Wang/LAKE/PPD/ABBOTT@ABBOTT, Damien  
Springue/LAKE/AI/ABBOTT@ABBOTT, James  
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Richard G  
Granneman/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject DDC slides

Attached are slides I am tentatively planning on presenting at the DDC next Thursday. Please comment.

Thanks  
Mike



A-429202 DDC presentation.i



HIGHLY CONFIDENTIAL  
ABBT0108742



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A-429202 DDC Presentation: Agenda

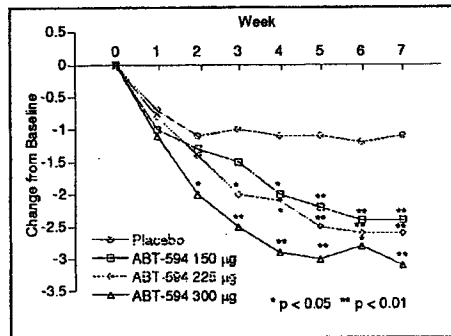
- Preclinical Characterization of A-429202 – Mike Meyer
- Pharmacokinetic Evaluation – Rick Granneman
- Clinical Development Plan – Joe Stauffer
- Commercial Assessment – Damien Springuel
- Summary – Mike Meyer

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## ABT-594 Has Validated NNR Pharmacology in Neuropathic Pain

- In Phase IIb trial in diabetic neuropathy, ABT-594 exhibited statistically significant and dose-dependent relief of pain

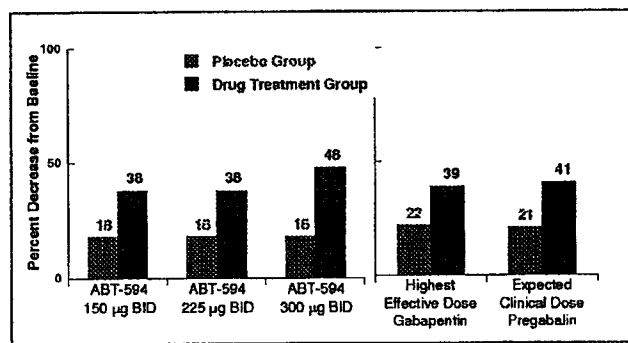


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## ABT-594 Has Validated NNR Pharmacology in Neuropathic Pain

- The level of efficacy achieved with ABT-594 is at a minimum comparable to the gold standard Gabapentin or its follow-on Pregabalin

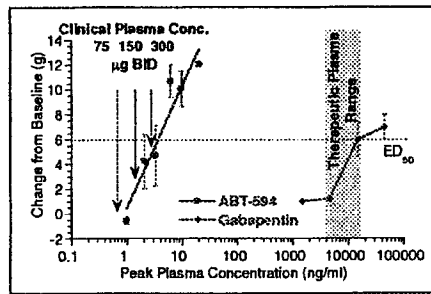


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## ABT-594 Has Validated NNR Pharmacology in Neuropathic Pain

- Plasma levels achieved in these dosing groups are consistent with plasma levels required to produce efficacy in preclinical models of neuropathic pain



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**ABT-594 May Have Efficacy in Acute and Chronic Nociceptive Pain**

- In molar extraction trial (acute pain), ABT-594 exhibited significant, albeit modest, analgesic activity at highest dosing group
  - May be limited by slow onset of action related to long  $t_{max}$
  - May be limited by non-optimal dosing form (powder in bottle)
  - Molar extraction model developed for NSAIDs
- In Phase IIa trial in pain associated with osteoarthritis, ABT-594 exhibited a trend toward efficacy at top dosing group
  - Evaluation of potential efficacy limited by low dosing range

*Neither clinical nor preclinical evidence preclude the use of  
NNR agonists in the treatment of nociceptive pain states*

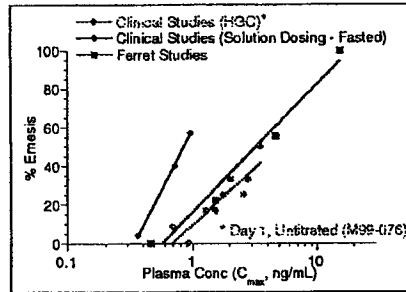


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### ABT-594 Was Discontinued from Clinical Development Based on an Unfavorable Side Effect Profile

- Key adverse events associated with ABT-594 were nausea, emesis and dizziness
- Preclinical models accurately predict plasma levels associated with emesis for ABT-594
- Significant differences in tolerability of ABT-594 exist based on formulation



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Requirements of Replacement for ABT-594

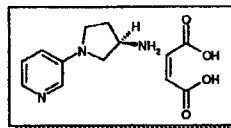
- Retention of comparable efficacy to ABT-594 in models predictive of efficacy in neuropathic and nociceptive pain states
  - Equivalent potency is NOT required
- A ten to thirty-fold improvement in therapeutic index relative to nausea and emesis
- Evidence/indications of less propensity to produce dizziness
- Pharmacokinetic profile consistent with BID dosing
- Acceptable safety profile:
  - Cardiovascular safety
  - CNS safety
  - Toxicology

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### Physical Properties

- Intrinsic Properties
  - Solubility > 14 mg/ml over pH range of 5.5 to 12
  - pKa = 6.1 and 8.8
  - Negative LogD through physiologic pH range
- Preferred salt: Maleate
  - M.W. = 279.29
  - Crystalline, m.p. = 180 C., no polymorphs identified
  - Dissolution rate (pH 6.8) 27 mg/minute/cm<sup>2</sup>
- Stability
  - Stable to visible light in solutions across wide pH range
  - Stable in solid form to visible and UV light
  - Thermal stability testing ongoing (phosphate buffer incompatibility discovered during initial evaluations)
- *Both a solid oral dosage and solution iv dosage formulation are feasible for first in man studies*



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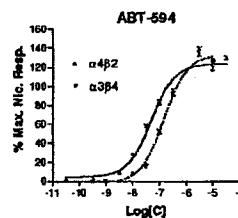
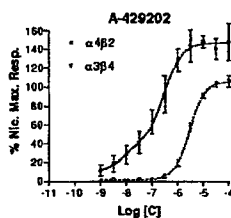
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*In Vitro* Pharmacology

- Receptor binding profile ( $K_i$ , nM):  
 ~ 3  $\mu$ M at  $\mu$ -opioid receptor

	$\alpha 4\beta 2$	$\alpha 7$	$\alpha 1\beta \gamma \delta$
A-429202	0.19	11,900	2000
ABT-594	0.04	610	500

- In Vitro Profile :



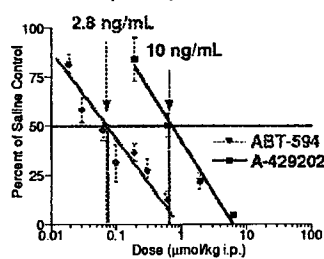
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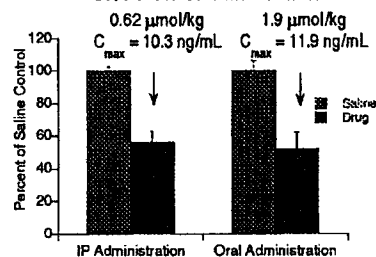
*In Vivo* Efficacy – Formalin Model of Nociceptive Pain

- $ED_{50} = 0.7 \mu\text{mol/kg}$ , i.p.
- Analgesic effects blocked by NNR antagonist mecamylamine, but not opioid antagonist naloxone
- Retains activity upon oral administration—equivalent plasma levels produce equivalent response

Dose-Response (IP Administration)



Oral vs. IP Administration



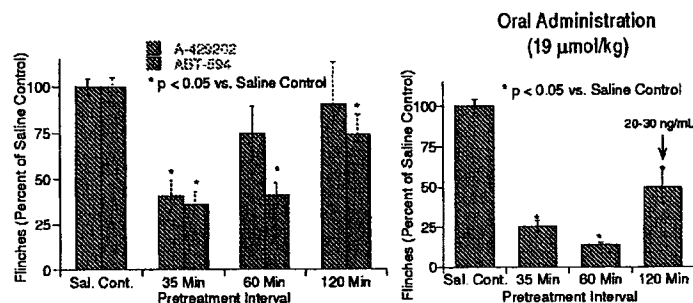


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## Formain Model: Duration of Action Studies

- A-429202 exhibits shorter duration of action than ABT-594
- Efficacy correlates with plasma levels

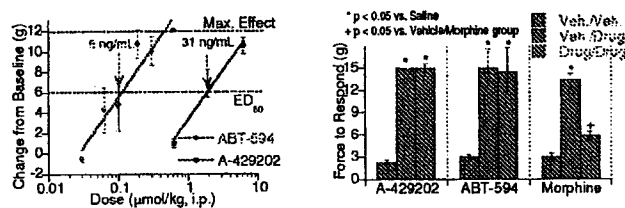


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*In Vivo* Efficacy – Chung Model of Neuropathic Pain

- $ED_{50} = 1.9 \mu\text{mol/kg}$ , i.p.
- Like ABT-594, retains efficacy upon repeated administration in a dosing protocol that produces tolerance to the effects of morphine

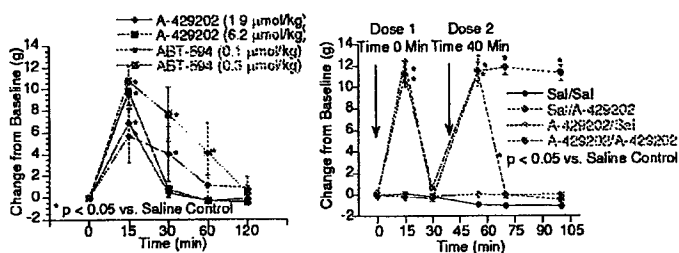


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## Chung Model: Duration of Action

- Both ABT-594 and A-429202 have a relatively short duration of action in Chung model, but A-429202 is shorter than ABT-594
- Full efficacy is re-established, and retained for >1 hr after second drug administration (no tachyphylaxis)



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## A-429202: Efficacy vs. Other Analgesics

	Persistent Nociceptive Pain	Neuropathic Pain – Acute Dosing	Neuropathic Pain – Repeat Dosing	Acute Thermal Pain
A-429202	+++	+++	+++	++
ABT-594	+++	+++	+++	+++
Morphine	+++	+++	+	++
Celecoxib	++	0	0	0
Gabapentin	+	++	N.D.	0

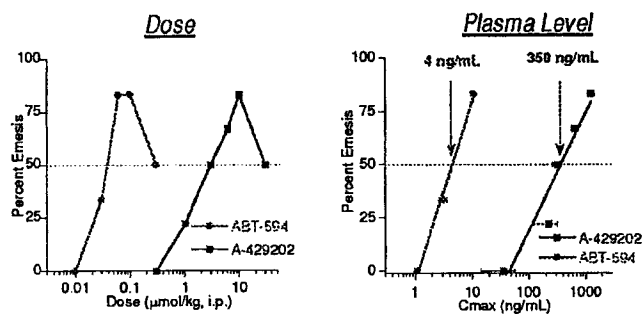
+++ is &gt;70% efficacy; ++ is 30-70% efficacy; + is &lt;30% efficacy; 0 is no activity.

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## Tolerability Profile – Emesis Liability in Ferrets (Acute Studies)

- A-429202 is approximately 100-fold less emetic than ABT-594 assessed either by dose or by plasma level



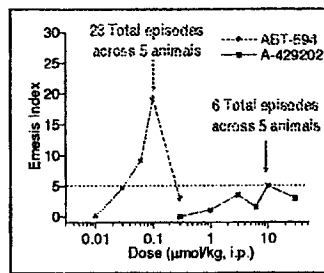


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## Tolerability Profile: Assessment of Emesis Severity

- Emesis Index: (Total # of emetic episodes times fraction of animals exhibiting emesis)
- Based on severity of emesis, the potency difference is greater than 100-fold

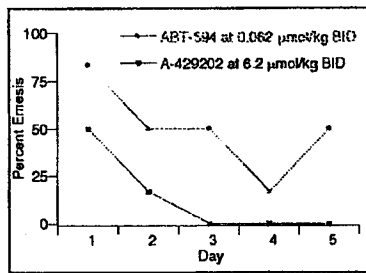


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Tolerability Profile - Emesis Liability in Ferrets  
(Repeat Administration Studies)

- Doses selected to be "equi-  
emetic" based on acute  
dosing studies
- At 6.2  $\mu\text{mol/kg}$ , A-429202 is  
fully efficacious in Formalin  
model and produces 80% of  
maximal response in Chung  
model
- At 0.062  $\mu\text{mol/kg}$ , ABT-594  
below 50% of full efficacy in  
both in Formalin and Chung  
models



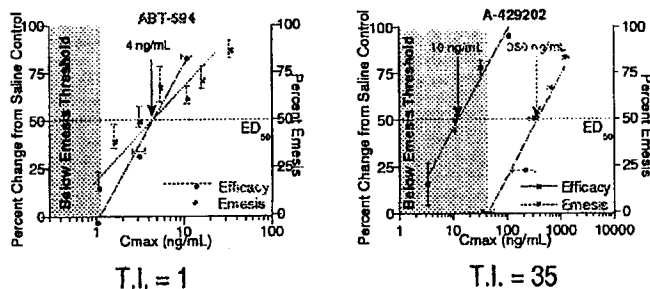
>100-Fold Potency Difference

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## Therapeutic Index - Efficacy in Nociceptive Pain vs. Emesis Liability

- A-429202 exhibits a 35-fold improvement in T.I. vs. ABT-594 based on peak plasma levels
- At a "no-emesis" plasma concentration, A-429202 exhibits ~80% of maximal efficacy

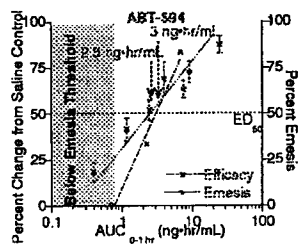


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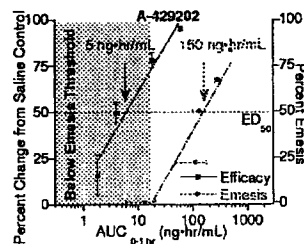
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## Therapeutic Index – Efficacy in Nociceptive Pain vs. Emesis Liability

- Both efficacy and emetic episodes are confined to the first hour of observation
- Calculation of therapeutic index based on  $AUC_{0-1hr}$  results in similar values



T.I. = 1.3



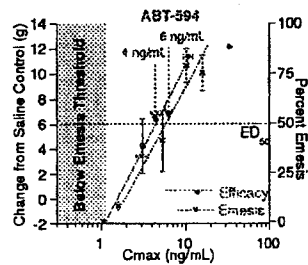
T.I. = 30

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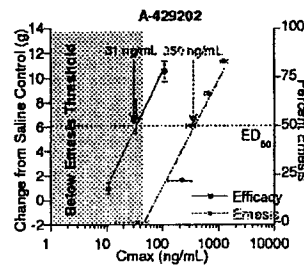
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## Therapeutic index – Efficacy in Neuropathic Pain vs. Emesis Liability

- In the Chung model, A-429202 exhibits a 16-fold improvement in T.I. Vs. ABT-594
- At a "no emesis" plasma concentration, A-429202 exhibits approximately 50% of maximal efficacy in neuropathic pain model



T.I. = 0.67



T.I. = 11



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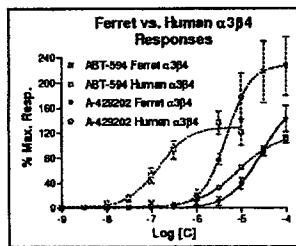
Is Improved T.I. for A-429202 an Artifact of Species Differences  
in Selectivity for NNR subtypes?

• Assuming  $\alpha 3\beta 4$  subtype mediates emesis:

- A-429202 exhibits comparable efficacy and potency at human and ferret  $\alpha 3\beta 4$  receptors
- ABT-594 exhibits greater potency, but lower efficacy at human vs. ferret  $\alpha 3\beta 4$  receptors
- Therefore, models may underestimate anticipated improvement in T.I.

• Assuming  $\alpha 4\beta 2$  subtype mediates efficacy:

- Radioligand binding (rat), DA release (rat), and human functional  $\alpha 4\beta 2$  response exhibit comparable selectivity ratios (5:1, 2:1, 3.6:1)
- Species differences in human vs. rat  $\alpha 4\beta 2$  are very small and would not be anticipated to affect T.I.



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Calculation of T.I. With Adjustment for *In Vitro* Species Differences

$$T.I. = \frac{\text{Emesis}}{\text{Efficacy}} \times \frac{\text{Human } \alpha 3\beta 4}{\text{Ferret } \alpha 3\beta 4^*} \times \frac{\text{Rat } \alpha 4\beta 2^{**}}{\text{Human } \alpha 4\beta 2}$$

$$\text{ABT-594} = \frac{4 \text{ ng/mL}}{4 \text{ ng/mL}} \times \frac{0.14 \text{ } \mu\text{M}}{4.7 \text{ } \mu\text{M}} \times \frac{0.037 \text{ nM}}{50 \text{ nM}} = 0.000022$$

$$\text{A-429202} = \frac{350 \text{ ng/mL}}{10 \text{ ng/mL}} \times \frac{8.7 \text{ } \mu\text{M}}{28 \text{ } \mu\text{M}} \times \frac{0.187 \text{ nM}}{180 \text{ nM}} = .011$$

T.I. Improvement (A-429202 vs. ABT-594):

Without Correction: 35x

With Correction: 513x

\* Ferret  $\alpha 3\beta 4$  receptor in oocyte expression system; human  $\alpha 3\beta 4$  receptor in stable cell line.\*\* Using rat brain cytosine binding as surrogate for rat  $\alpha 4\beta 2$

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Calculation of T.I. With Adjustment for *In Vitro* Species Differences

$$T.I. = \frac{\text{Emesis}}{\text{Efficacy}} \times \frac{\text{Human } \alpha 3\beta 4}{\text{Ferret } \alpha 3\beta 4^*} \times \frac{\text{Rat } \alpha 4\beta 2^{**}}{\text{Human } \alpha 4\beta 2}$$

$$\text{ABT-594} = \frac{4 \text{ ng/mL}}{4 \text{ ng/mL}} \times \frac{0.14 \text{ } \mu\text{M}}{4.7 \text{ } \mu\text{M}} \times \frac{7.0 \text{ nM}}{50 \text{ nM}} = 0.0042$$

$$\text{A-429202} = \frac{350 \text{ ng/mL}}{10 \text{ ng/mL}} \times \frac{8.7 \text{ } \mu\text{M}}{28 \text{ } \mu\text{M}} \times \frac{13 \text{ nM}}{180 \text{ nM}} = 0.79$$

T.I. Improvement (A-429202 vs. ABT-594):

Without Correction: 35x

With Correction: 187x

\* Ferret  $\alpha 3\beta 4$  receptor in oocyte expression system; human  $\alpha 3\beta 4$  receptor in stable cell line.\*\* Using DA release as surrogate for rat  $\alpha 4\beta 2$

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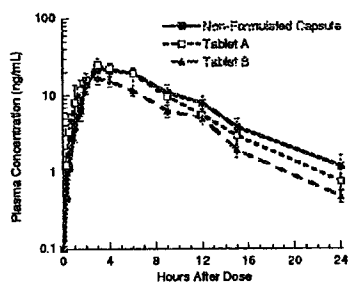
## Pharmacokinetics Summary: ABT-594, ABT-089 vs. A-429202

		IV Dose				Oral Dose	
		$t_{1/2}$	CLp	Vc	V $\beta$	$t_{1/2}$	%F
Rat	ABT-594	1.5	1.7	3.5	1.5	2.1	13%
	ABT-089	1.1	3.4	3.0	5.5	3.5	33%
	A-429202	2.0	5.1	7.8	15.4	2.1	52%
Monkey	ABT-594	1.4	1.7	2.7	3.5	NI	60%
	ABT-089	2.2	1.9	2.0	5.1	1.7	26%
	A-429202	0.7	1.7	1.1	2.0	1.2	22%
Dog	ABT-594	1.7	3.4	1.5	4.1	3.2	24%
	ABT-089	1.8	2.0	2.9	5.0	1.7	61%
	A-429202	1.9	2.7	2.8	7.8	1.9	39%

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## Solid Formulation in Dog Improve Bioavailability and Half-Life



	%F	t <sub>1/2</sub>
Non-Formulated Capsule	106%	3.6 h
Tablet A	93%	3.7 h
Tablet B	75%	3.8 h

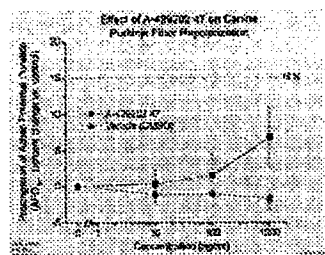
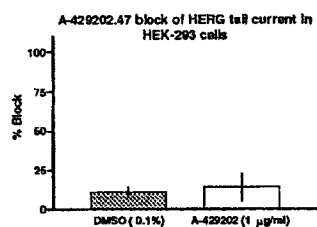


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## Cardiovascular Safety – hERG Interaction

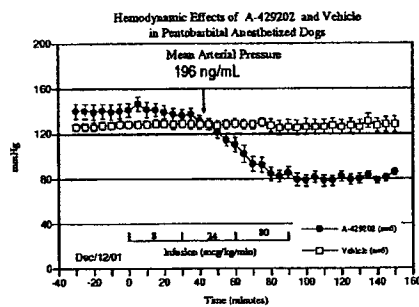
- In vitro characterization: at 1  $\mu\text{g/ml}$  (30 to 100 fold above therapeutic plasma concentration):
  - No effects on hERG tail currents
  - ~7% increase in action potential in canine purkinje fiber assay



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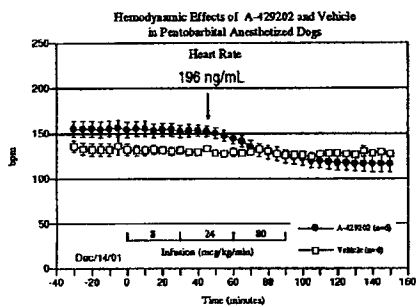
## Cardiovascular Safety -- Mean Arterial Pressure



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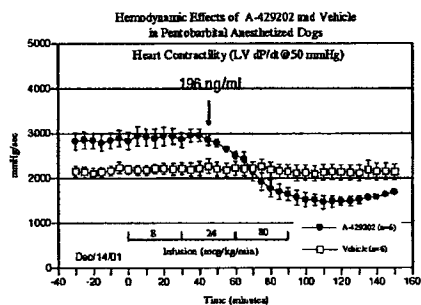
Cardiovascular Safety – Heart Rate



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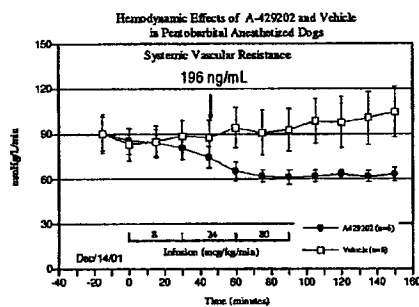
## Cardiovascular Safety – Heart Contractility



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## Cardiovascular Safety – Systemic Vascular Resistance





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Cardiovascular Safety – Unchanged Parameters

- Pulmonary arterial pressure
- Pulmonary vascular resistance
- Central venous pressure
- Left ventricular end diastolic pressure
- Core temperature
- QTc interval

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CNS Safety Pharmacology

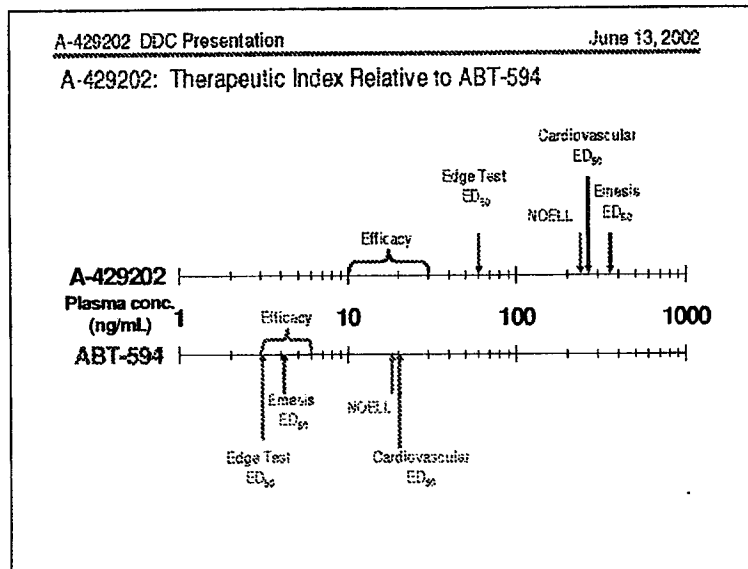
- A-429202 exhibits improved therapeutic index in two models of balance and coordination relative to ABT-594
  - Rat edge test
  - Rat rotarod test
- A-429202 exhibits improved therapeutic index in model of seizure threshold in mice
- Comparable therapeutic index observed for effects on:
  - Spontaneous motor activity
  - Body temperature
  - LD<sub>50</sub>
- Similar mild stimulant-like profile observed in slow wave EEG

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Toxicology

- Ames, micronucleus negative
- In rat 2-week toxicology study:
  - The no-observable- adverse-effect level (NOAEL) was 30 mg/kg/day
  - Plasma levels (AUC) at this dose were approx. 5000 ng•hr/mL and were comparable at day 0 and day 13
  - Efficacy (ED<sub>50</sub>) in Chung model of neuropathic pain achieved at AUC of 66 ng•hr/mL (75 fold below NOAEL level)



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A-429202: Summary of Preclinical Profile

- Comparable efficacy profile to ABT-594 in models of neuropathic and nociceptive pain
  - Only significant difference occurs in model of acute thermal pain
- At a minimum, exhibits a 10-30 fold improvement in therapeutic index in model of nausea and emesis
- Good oral bioavailability across multiple species
  - Profile consistent with BID dosing in humans
  - Potential metabolism concerns will be dependent upon degree to which metabolism vs. renal clearance govern drug elimination
- Safety profile:
  - Comparable CV profile to ABT-594
  - Comparable or improved CNS safety profile to ABT-594
  - No significant issues identified from 2-week toxicology study



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**Key Development Issues**

- Establishing sufficient level of tolerability at a target plasma concentration
  - Can plasma level serve as surrogate marker for Go/No Go decision?
- Pharmacokinetics and metabolism:
  - Sufficient half life for BID dosing
  - Metabolism by a singly CYP isoform
  - Clearance in renally impaired population
  - Is  $t_{max}$  consistent with consideration for treatment of acute pain?
- If GI tolerability is significantly improved will other adverse events now become dose limiting?
  - Dizziness
  - Sleep Disturbance
- Abuse and/or addiction potential
  - Re-initiation of tobacco use or treatment for nicotine dependence

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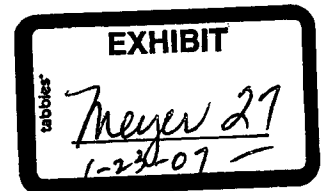
**Acknowledgments**

- In Vitro Pharmacology
  - Carol Suraw
  - Dave Anderson
  - Clark Biggs
  - Jerry Budzik
  - Ying-Jun Cao
  - Gilles Dube
  - Dave McKenna
  - Brent Putman
  - Pamela Puttlarcken
- Chemistry
  - Bill Bunnelle
  - Anwer Basha
  - Mick Dart
  - Meghan Gallagher
  - Jianguo Ji
  - Tao Li
  - Jennifer Pace
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- Development
  - Joseph Stauffer
  - Daaron Dotier
  - Cindy Batiste
- Commercial
  - Danhui Wang
  - Damien Springuel

# Meyer Deposition Exhibit 27

## P's Exhibit GN – Part 1

DDC: A-429202  
Neuronal Nicotinic Receptor (NNR) Agonist  
June 13, 2002

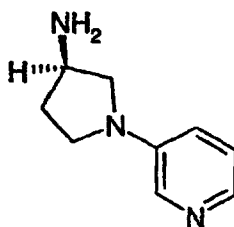


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**Neuronal Nicotinic Receptor (NNR) Agonist**

**A-429202**



**(R)-1-(3-Pyridinyl)-3-pyrrolidinylamine**

**DISCOVERY DEVELOPMENT CANDIDATE**

**June 13, 2002**

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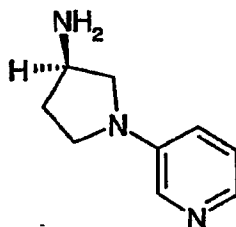
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**Neuronal Nicotinic Receptor (NNR) Agonist**

**A-429202**



**(R)-1-(3-Pyridinyl)-3-pyrrolidinylamine**

**DISCOVERY DEVELOPMENT CANDIDATE**

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## I. Executive Summary

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Despite this, there have been few major advances in pain therapy over the past several decades, and pain management continues to rely on non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and adjuvant analgesics. Although many segments of the patient population are well served with existing analgesic agents, there exist significant areas of unmet need. For example, many chronic pain conditions, and in particular neuropathic pain states, are poorly managed with existing agents. Substantial tolerability and safety issues exist with opioid therapy. NSAIDs and COX-2's are of limited utility in the treatment of all but mild to moderate pain, and even the well-tolerated COX-2's have safety issues with chronic use.

ABT-594 is a novel non-opioid, non-NSAID analgesic that has demonstrated clinical efficacy in the treatment of acute and chronic nociceptive pain and in the treatment of neuropathic pain. ABT-594 has provided clinical validation to the neuronal nicotinic receptor (NMR) agonist pharmacology as a novel mechanism for the treatment of pain. However, ABT-594 was poorly tolerated, particularly with respect to the side effects of nausea and emesis. The requirements for a backup to ABT-594 were clearly defined by the clinical experience. A successful follow-on to ABT-594 must exhibit comparable broad-spectrum efficacy, must exhibit a pharmacokinetic and metabolism profile consistent with no more frequent than twice daily dosing, and must exhibit a 10 to 30-fold improvement in therapeutic index with respect to nausea and vomiting.

A-429202 ((R)-1-(3-pyridinyl)-3-pyrrolidinylamine) is a novel NMR agonist that retains a similar analgesic profile to ABT-594, but with an overall net improvement in therapeutic index relative to nausea and emesis ranging from 10 to 50-fold. A-429202 exhibits high affinity ( $K_i = 0.187$  nM) for and shows full functional efficacy at the  $\alpha 4\beta 2$  NMR, ( $EC_{50} = 0.18$   $\mu$ M) and exhibits approximately 10-fold greater selectivity for  $\alpha 4\beta 2$  over  $\alpha 3\beta 4$  receptors than ABT-594. A-429202 demonstrates efficacy comparable to ABT-594 in multiple models of nociceptive and neuropathic pain. Like ABT-594, A-429202 retains efficacy upon repeated dosing under experimental protocols where tolerance develops to the analgesic effects of morphine. A-429202 is active after both i.p. and oral administration, and efficacy is correlated to drug plasma levels. Efficacy ( $ED_{50}$ ) is achieved at plasma levels of 10 to 30 ng/mL, whereas ABT-594 exhibits efficacy in the range of 3 to 6 ng/mL. In the ferret model of emesis liability, A-429202 is significantly less emetic than ABT-594, and exhibits a more complete attenuation of emesis and nausea behavior after repeated administration. A-429202 requires plasma concentrations of approximately 350 ng/mL to produce emesis ( $ED_{50}$ ) in the ferret, whereas ABT-594 produces emesis ( $ED_{50}$ ) at approximately 4 ng/mL. Importantly, the preclinical data suggest that it is possible to achieve >50% efficacy in neuropathic and nociceptive pain at plasma levels where no emesis is observed.

A-429202 is rapidly cleared from rat, dog and monkey after i.v. administration, with half life ranging from 0.7 to 2.0 hours and  $CL_p$  ranging from 1.7 to 5.1 L/hr·kg. Oral bioavailability ranges from 22% in monkey to 52% in rat. In the rat, AUC values are relatively linear across dose, and concentrations do not accumulate significantly after repeated dosing. In rat, A-429202 partitions into the brain, with peak concentrations 5-6 fold higher than in the plasma. The elimination half-life from the brain is 6-7 hours.

In the rat, A-429202 is largely renally cleared, with 54% of total radioactivity excreted in the urine, of which approximately 50% is parent drug. *In vitro* metabolism studies in rat, dog, and human microsomes and hepatocytes indicate a predominant role for phase I metabolism. These studies, however, suggest additional clearance mechanisms (e.g. renal and/or secretion) are likely to have a strong impact on total drug clearance. Cytochrome P450 interaction studies show that the CYP2D6 isoform is largely responsible for the metabolism of A-429202. Although A-429202 is an inhibitor of CYP2D6, the effect is weak at anticipated therapeutic plasma concentrations of 10 to 30 ng/mL, and significant drug-drug interactions due to CYP2D6 inhibition by this agent are not anticipated.

Human pharmacokinetic behavior has been projected with physiologically-based models and Trial Simulator. With predicted 70% absorption efficiency, 80% survival from hepatic first pass clearance, a human clearance of 46 L/hr and a terminal phase half life of 6 to 10 hours are predicted, a profile consistent with twice daily dosing.

A-429202 was neither mutagenic nor toxic when tested in a bacterial reverse mutation assay up to concentrations of 2000  $\mu$ g/well. Moreover, A-429202 was not clastogenic when evaluated in an *in vitro* micronucleus assay at concentrations up to 1000  $\mu$ g/mL. Both assays were conducted in the presence and absence of metabolic activation. In a two-week toxicity study in rats, daily oral administration of A-429202 was well-tolerated at dosages up to 30 mg/kg/day as determined by clinical signs, body weight, food consumption, organ weights, gross necropsy, histopathologic evaluation of tissues, hematology and

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clinical chemistry measurements. In additional assays of CNS-related adverse events, A-429202 exhibited an improved therapeutic window relative to ABT-594 in models of balance and coordination, and in models of seizure threshold.

Hemodynamic studies in the anesthetized dog indicate that A-429202, at plasma concentrations up to 5-fold therapeutic, produced no changes in any measured cardiovascular parameters. At plasma concentrations up to 30-fold therapeutic, A-429202 produced self-limiting decreases in blood pressure, heart rate, contractility and systemic vascular resistance. The overall hemodynamic profile of A-429202 is consistent with that of ABT-594, which displayed no clinically meaningful cardiovascular effects during its development. A-429202 produced no effects on QTc interval *in vivo*, did not affect the duration of action potential of canine cardiac Purkinje fibers *in vitro* at concentrations 100-fold above therapeutic plasma concentrations, and did not affect hERG tail currents *in vitro* at concentrations 100-fold above an efficacious plasma concentration.

The goal of the Transition Team development program will be to A) establish whether the pharmacokinetics of A-429202 are consistent with BID dosing; B) evaluate tolerability at a target plasma concentration of 10 to 30 ng/mL that has been defined by the preclinical experiments as an efficacious plasma concentration; and C) evaluate the effects of various pharmacokinetic parameters on tolerability (in particular the effects of rate of rise on emesis and nausea). To meet these goals, the Transition Team envisions the use of both oral capsule and parenteral dosage forms. This will allow determination of absolute bioavailability, development of an optimal PK profile to minimize GI-related adverse events, and elimination of the uncertainty brought about by the significant difference in tolerability between oral solution dosing and capsule dosing encountered during the development of ABT-594.

A U.S. patent application was filed on May 21, 1999, with a C.I.P. filing on April 26, 2000, claiming composition of matter for A-429202. The World Application (WO 00/71534 A1) published on November 30, 2000. The projected patent protection in the U.S. extends to May 21, 2020, while ex-U.S. coverage extends to May 15, 2020.

A-429202 falls under the existing research agreement with NeuroSearch (Denmark), and is designated as a "collaboration compound". As such, a series of milestone payments will be associated with the clinical development of A-429202, the first being a payment of \$1.5 million to NeuroSearch following first time in man.

A-429202 is a follow-on replacement compound for ABT-594 that meets the clinically defined requirements of retention of efficacy across a range of preclinical models and decreased emesis and nausea liability as assessed in preclinical models. The improved therapeutic index that may be achievable clinically with this agent can potentially expand its usefulness into a broad range of patient populations. An NNR agonist such as A-429202, with a significantly wider therapeutic index than ABT-594, will permit a full evaluation of the "preclinical promise" that NNR agonists represent a new class of analgesic agents.

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## II. Medical Need

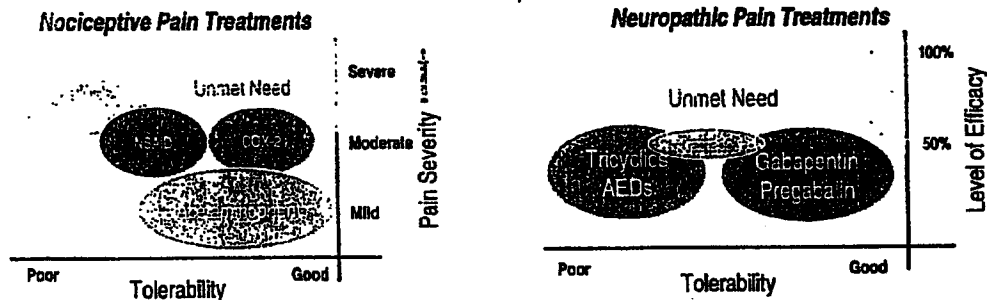
Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is always subjective; no neurophysiological or chemical test can measure pain. Pain is commonly segmented by duration (acute vs. chronic), intensity (mild, moderate, and severe), and type of pain (nociceptive vs. neuropathic)(Table 1).

Table 1. Pain Segmentation Matrix

Duration	Type of Pain	Severity of Pain		
Acute	Nociceptive	Mild	Moderate	Severe
Chronic	Nociceptive			
	Neuropathic			

**Nociceptive pain** is the most well known type of pain, and is caused by tissue injury detected by nociceptors at the site of injury. Nociceptors are activated by stimuli that are potentially able to damage tissue, so-called noxious stimuli. After the injury, the site becomes a source of ongoing pain and tenderness. This pain and tenderness are what clinicians expect to encounter; it is considered "acute" nociceptive pain. This pain and tenderness gradually diminish as healing progresses and disappear when healing is complete. Examples of acute nociceptive pain include surgical procedures (post-op pain) and bone fractures. Even though there may be no permanent nerve damage, "chronic" nociceptive pain results from some conditions when pain extends beyond six months. Examples of chronic nociceptive pain include osteoarthritis, rheumatoid arthritis, and musculoskeletal conditions (e.g., back pain), cancer pain, etc.

Whereas mild to moderate nociceptive pain and even severe acute nociceptive pain are well managed by existing therapies, the treatment of chronic moderate to severe pain remains an area of significant unmet need. The effectiveness of NSAIDs is marginal for moderate to severe pain, and side-effect profiles can limit their use in certain patient populations. Use of opioids for chronic pain management is limited by the development of tolerance and constipation, and the stigma of addiction potential. Monitoring requirements, cumbersome delivery systems, inconvenient dose schedules and issues related to controlled substances further complicate the clinical application of these currently available tools<sup>1</sup>. Clinical experience suggests that the effects of drug classes such as steroids, NSAIDs, opioids, antidepressants, and muscle relaxants are transient, often having limited effectiveness, with little or no positive effects on disability and quality of life<sup>2</sup>.



**Neuropathic pain** is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (IASP). Neuropathic pain is not associated with nociceptive stimulation, although the passage of nerve impulses that is ultimately perceived as pain by the brain is the same in both nociceptive and neuropathic pain. The term neuropathic pain encompasses a wide range of pain syndromes of diverse etiologies. The three most commonly diagnosed pain types of neuropathic nature are diabetic neuropathy, cancer neuropathy, and HIV pain. In addition, neuropathic pain is diagnosed in patients with a wide range of other disorders, including trigeminal neuralgia, post-herpetic neuralgia, traumatic neuralgia, phantom limb, as well as a number of other disorders of ill-defined or unknown origin.

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Currently, there is no FDA-approved drug for the treatment of neuropathic pain. Neurontin (gabapentin) is approved for painful diabetic neuropathy in the UK. Two drugs have labels for a specific type of neuropathic pain: Tegretol for trigeminal neuralgia, Lidoderm for post-herpetic neuralgia. Numerous drugs are prescribed off-label to manage neuropathic pain, with leading classes being tricyclic anti-depressants (TCA's), anticonvulsants, SSRIs, and NSAIDs. Neuropathic pain is poorly managed by any of the existing drug treatments, with nearly 50% of patients achieving no meaningful pain relief from the "gold standard" Neurontin.

Despite significant advances, inadequate pain management across the spectrum of pain etiologies remains a major public health problem. Both patients and clinicians are seeking improved pain management, and accrediting agencies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) are demanding improved strategies<sup>3,4,5,6</sup>. The goal of pain management is not necessarily absolute pain relief (anesthesia), for this typically comes at the cost of significantly reduced function. Therefore, rather than thinking of pain medications as cure-all, we should consider them tools inside a pain management toolbox. The more tools one has available, the better the outcome is likely to be<sup>7</sup>. The overwhelming financial success, despite marginal clinical efficacy, of Neurontin in the treatment of neuropathic pain syndromes illustrates the critical need for better drugs, and the acceptance by physicians and patients of an "analgesic" with a novel (and not entirely understood) mechanism of action. The same may be said for *bridging drugs* like tramadol. Going forward, the development of novel therapeutics for the treatment of pain can only help in the ongoing struggle to balance safety and efficacy for those patients most in need.

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### III. Market Overview

Pain is a universal experience that is often episodic and self-limiting, requiring only short-term treatment with OTC or prescription analgesics. Some acute episodes of pain persist, however, and can result in changes in the nervous system that result in chronic pain long after the initial insult<sup>6</sup>. According to the National Institutes of Health, pain costs Americans more than \$100 billion each year in health care costs and lost productivity.

Pain and its management, encompasses a vast range of experiences, diseases, and treatments. Because pain is such a broad, ill-defined and subjective diagnosis, members of the medical community have historically distanced themselves from fully acknowledging the magnitude of this challenge. The total pain management market can be divided into a number of sectors, including:

1. Pharmaceutical market
  - a. Prescription
    - NSAIDs/COX-2s
    - Non-opioids (acetaminophen, tramadol)
    - Opioids
    - Adjuvants
  - b. Over-the-Counter (OTC)
2. Devices market
  - a. Patient controlled analgesia
  - b. Transcutaneous electrical nerve stimulation (TENS)
3. Services market
  - a. Home care
  - b. Hospices

This commercial assessment focuses on the "Prescription" pain market. Pain medications are prescribed according to the pain type and intensity (Figure 1). It is estimated that a little over one-third of all pain prevalence in the US is actually treated - approximately 87 million Americans every year are treated for pain, out of a 236 million prevalence (Table 2). The total prevalence of pain outside the US is not well documented; however, the total treated pain population in the ex-US is estimated at around 145 million.

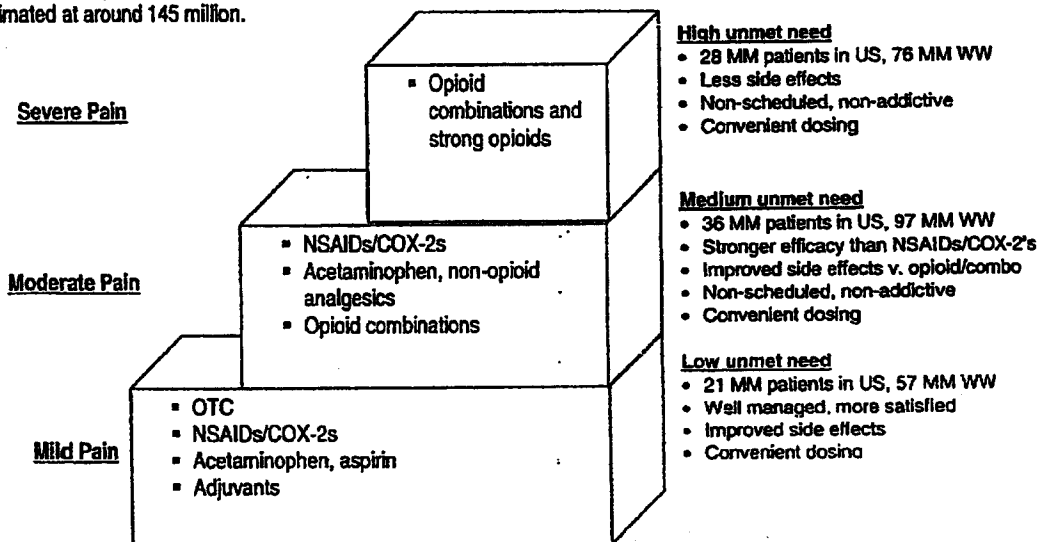


Figure 1. World Health Organization Three-Step Analgesic Ladder

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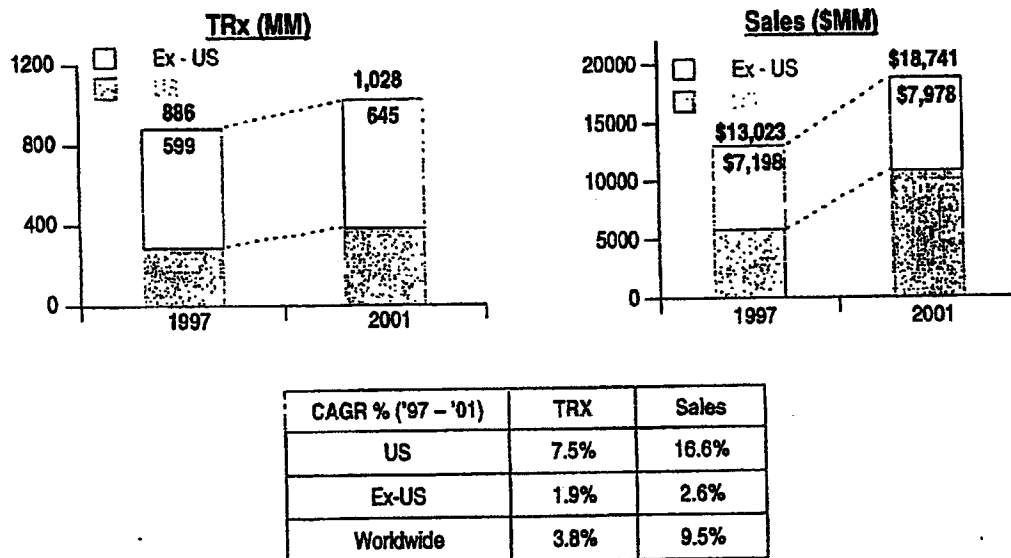
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Table 2. Estimated Treated Population by Segment in US (MM)

Duration	Condition	Prevalence	Rx Treatment Rate	Treated Patients
Acute	Post operative	29	100%	29
	Acute musculoskeletal/Trauma	118	19%	22
	Other Acute (visceral, obstetric, etc.)	19	37%	7
	<b>Subtotal Acute</b>	<b>185</b>	<b>31%</b>	<b>58</b>
Chronic	Cancer pain	1.5	100%	1.5
	Arthritis	25	60%	15
	Musculoskeletal	15	57%	8.5
	Other	2	75%	1.5
	<b>Subtotal Chronic Nociceptive</b>	<b>43.5</b>	<b>61%</b>	<b>26.5</b>
	<b>Neuropathies</b>	<b>7.5</b>	<b>33%</b>	<b>2.5</b>
<b>All Pain Total</b>		<b>236</b>	<b>37%</b>	<b>87</b>

Sources: National Center for Health Statistics, Decision Resources, Datamonitor, etc.

The prescription pain market achieved worldwide sales of \$18.7 billion in 2001 (excluding anti-migraine drugs and local anesthetics). A compounded annual growth rate (CAGR) of 9.5% in worldwide sales is supported by the changes in demographics (i.e., aging population), increased awareness for more aggressive pain management, and new product launches. Particularly in the US, a 16.6% sales CAGR in the past 5 years is primarily driven by the introduction of Ultram (a non-opioid analgesic by J&J), OxyContin (oxycodone by Purdue), and the COX-2 class (Celebrex by Pharmacia and Vioxx by Merck). It is estimated that acute pain conditions contribute to approximately 65% of all pain medication prescriptions but 30% of sales (Figure 2).



Sources: IMS DataView

Figure 2. Pain Rx TRx and Sales 1997 - 2001

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**A. Nociceptive Pain:**

The pharmacological classes of drugs most frequently prescribed for the treatment of nociceptive pain are NSAIDs, non-opioid/non-NSAID analgesics, opioids, and to a lesser extent various adjuvants. Approximately 25% of all treated nociceptive pain is described as mild, 42% as moderate, and 33% as severe, respectively (Table 3 and Table 4). Severity for neuropathic pain is not well defined or tracked at this point of time.

**Table 3. Nociceptive Pain Segmented by Pain Severity in US (MM).**

Type \ Severity	Acute Pain		Chronic Pain		TOTAL	
	# Patients	%	# Patients	%	# Patients	%
Mild Pain	17	30%	4	15%	21	25%
Moderate	21	35%	15	55%	36	42%
Severe	20	35%	8	30%	28	33%
TOTAL	58	100%	27	100%	85	100%

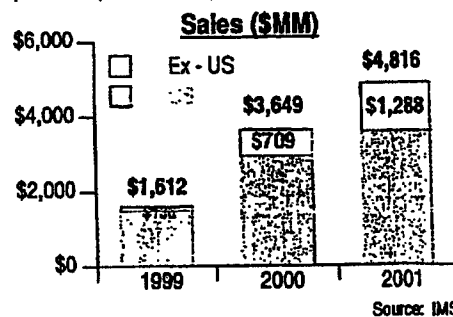
**Table 4. Nociceptive Pain Segmented by Pain Severity Worldwide (MM).**

	US	Ex-US	WW	%
Mild	21	36	57	25%
Moderate	36	61	97	42%
Severe	28	48	76	33%
TOTAL	85	145	230	100%

Numbers may reflect rounding.

Sources: National Center for Health Statistics, Decision Resources, Datamonitor, etc.

**NSAIDs:** Non-steroidal anti-inflammatory drugs have analgesic and anti-inflammatory activity. NSAIDs act peripherally to provide their analgesic effect by interfering with the synthesis of prostaglandins, through the inhibition of cyclooxygenase (COX). Most NSAIDs are non-selective inhibitors of the COX enzyme, and they are referred as "traditional NSAIDs". Traditional NSAIDs include ibuprofen, naproxen, and diclofenac. Although traditional NSAIDs are effective in managing moderate pain, their analgesic ceiling effect limits their use in more severe types of pain. In addition, GI adverse events are a well-documented concern with these products. COX-2's, like Celebrex (celecoxib) and Vioxx (rofecoxib), are newer NSAID compounds that selectively inhibit the COX-2 enzyme and appear to have fewer toxicities that result from the inhibition of COX-1, like gastrointestinal tract problems. Overall, COX-2 inhibitors are comparable to traditional NSAIDs in efficacy but have a more favorable GI profile. Three years post-launch, the COX-2 class, with 2 products – Celebrex and Vioxx, has become a \$5 billion market worldwide in 2001 (Figure 3). Many consider the improvement in GI profile realized by the COX-2 class just marginal; however, COX-2 as a sub-class has achieved 47% share of the overall NSAID class (incl. both traditional NSAIDs and COX-2's) in the US (Figure 4). Much lower penetration of COX-2's in the Ex-US can be explained by more restrictive government treatment guidelines and reimbursement policies.

**Figure 3. World-wide COX-2 Sales (\$MM).**

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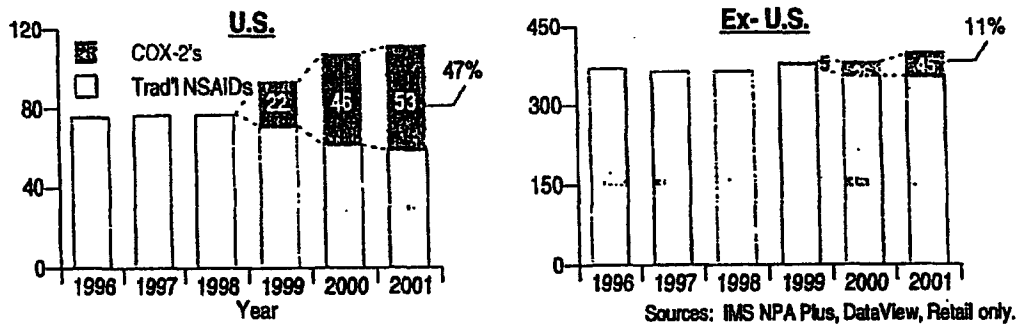


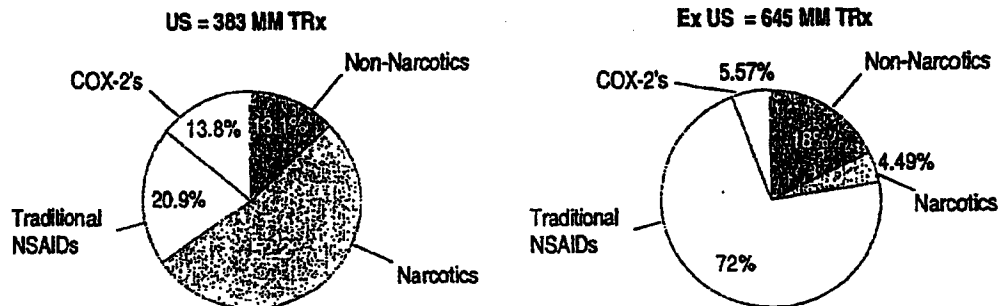
Figure 4. NSAID TRx in Retail Channel – Traditional and COX-2's (MM).

**Non-opioid analgesics:** Other analgesics, such as acetaminophen, and tramadol, are also commonly prescribed. These agents differ from opioid analgesics in the following way:

- There is a ceiling effect to analgesia;
- They do not appear to produce tolerance or physical or psychological dependence.

Non-opioid analgesics also differ from NSAIDs. They have no anti-inflammatory activity and no potential for prostaglandin-mediated side effects.

**Opioid analgesics:** Opioid analgesics are classified as agonists, mixed agonists-antagonists, or partial agonists by their activity at opioid receptors. Opioids' potent analgesic efficacy has long been proven; their side effects include GI motility impairment (e.g., constipation), respiratory depression, dependency, nausea and emesis. Morphine, fentanyl, oxycodone, and codeine bind with certain receptors (Mu, Kappa, Delta) in the CNS and peripheral tissues to provide analgesic effects. Mu receptors provide central analgesia, but also play a role in the development of respiratory depression, physical dependence and withdrawal symptoms. Kappa receptors are responsible for analgesia at the level of the spinal cord and the brain, but have less of a role in physical dependence and withdrawal. Delta receptors are concentrated in the substantia gelatinosa of the dorsal horn and have a primary effect upon spinal and supraspinal analgesia. While opioid analgesics are the leading class of pain medications in the US, the Ex-US pain market is dominated by traditional NSAIDs (Figure 5).



Sources: IMS DataView

Figure 5. Pain Medication TRx in 2001

**Adjuvants:** Adjuvant drugs are used in combination with non-opioid and opioid drugs to enhance pain management, and are used more frequently in complicated neuropathic pain syndromes (see following section). Adjuvant drugs include a variety of classes – anticonvulsants, antidepressants, etc.

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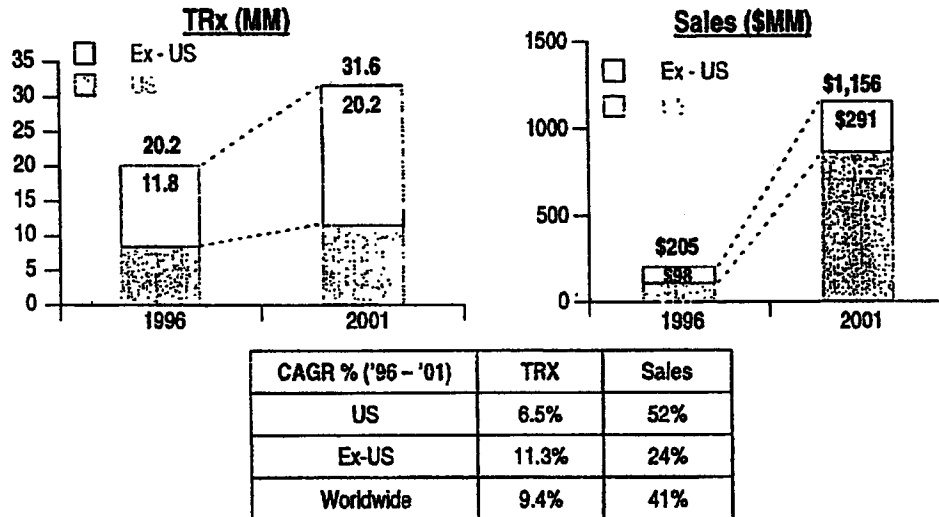
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**B. Neuropathic Pain:**

In the US, Neurontin has become the gold standard therapy for neuropathic pain, while in Europe, TCA's are still considered as the first line of product choice. The situation in Europe is believed primarily driven by cost-containment rather than product efficacy, since Neurontin is over 10 times more expensive than generic TCA's. The neuropathic pain medication market exceeded \$1 billion in sales in 2001. The rapid increase in total sales within the U.S. is driven largely by Neurontin sales, estimated to be approximately \$500 million (Figure 6). Since complete and sustained pain relief with the majority of the patients occurs infrequently, medication switching and cocktail approach are commonly seen in neuropathic pain management. Primary market research on ABT-594 in 2001 revealed that an average neuropathic pain patient takes at least 2 medications at any given time for the condition.



Sources: IMS Dataview, Scott Levin, Team Analysis

Figure 6. Neuropathic Pain Rx TRx and Sales 1996 - 2001

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#### IV. Market Drivers

Old lines of therapies such as NSAIDs, opioids and opioid combinations have long dominated the global pain management market. Generic products are widely used; no mechanistically novel therapies have emerged in decades. The success of Ultram, OxyContin, Celebrex, Vioxx, and Neurontin (Table 5) has proven that new compounds, even those lacking a new mechanism of action, can achieve tremendous commercial success even with just marginal improvement in clinical benefits.

Table 5. Recent New Product Launches in Pain Management

Brand	Class	2001 WW Sales (\$MM)	Launch	Company
Ultram	Non-opioid analgesic	592	1995	J&J
OxyContin	OxyCodone (Codeine & Combo)	1,429	1996	Purdue
Celebrex	COX-2	2,577	1999	Pharmacia/Pfizer
Vioxx	COX-2	2,176	1999	Merck
Neurontin Total	Anti-epileptic	1,703	1994	Pfizer
Neurontin in neuropathic pain	Anti-epileptic	495	1994	Pfizer

Sources: IMS Dataview, Scott Levin, Team Analysis

The neuropathic pain market is modest in size relative to the nociceptive pain market; however, it is critically under-served and its potential is largely untapped. One of the areas of greatest unmet medical need in the pain management field is for more effective therapies for the treatment of neuropathic pain:

- Improved efficacy: partial pain relief is the norm, and polypharmacy is often required to manage pain.
- Improved responder rates: typically only 40% to 60% of patients respond to any given treatment.
- Improved tolerability: TCA's, AED's, opioids have troublesome side effects that do not diminish over time.
- More convenient dosing: Most AED's (including Neurontin) and TCA's are typically dosed TID.
- Titration reduction: TCA's and AED's require longer than 4-week-titration period in order to minimize side effects and to reach an effective dose.

The treatment of moderate to severe chronic non-malignant pain is frequently inadequate because NSAIDs are not efficacious enough to provide complete relief and the use of opioids is limited due to addiction potential, abuse liability, tolerance and GI side effects (constipation, nausea, vomiting). Approximately 75% of all pain treated is considered as moderate to severe pain, and huge potential exists for new drugs that offer:

- Opioid-like efficacy,
- Without opioid-like side effects
  - Improved GI tolerability
  - Non-scheduled
  - Non-addicting

Key drivers of this market include unmet need, aging population, cost containment, and heavy marketing and sales spend (Table 6).

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Table 6. Key Market Drivers of Pain Management Market

Driver	Description
Unmet Medical Needs	Addressing the limitations in the clinical performance of a drug: <ul style="list-style-type: none"> <li>▪ Poor efficacy, i.e., with neuropathic pain.</li> <li>▪ Negative side effects: i.e., with traditional NSAIDs and opioids.</li> <li>▪ Lack of value-added formulations.</li> <li>▪ Abuse potential with opioid-based drugs.</li> </ul>
Demographics	Aging of the so-called "baby-boomer" generation combined with increased life spans is resulting in a change of the population age distribution – which corresponds to greater prevalence in conditions (e.g. diabetes, cancer) where pain therapeutics are indicated and increased overall market.
Increased Marketing	Similar to other therapeutic areas, heavy promotion, including large sales forces, aggressive professional and consumer marketing, has been the most visible aspect of large pharmaceuticals' tactics to drive sales of new drugs.
Under Treatment	The incomplete penetration of the overall pain population is being addressed as under treatment of pain and is recognized as substandard care and reservations on aggressive pain management fade.
Healthcare Cost Pressure	Similar to other therapeutic areas, under ever increasing financial pressure from growth in prescription benefit costs, payer groups seek to control spending on all drugs, including pain therapies – one of the outcomes is increased patient out-of-pocket cost for drug benefit, which will make lower-priced older brands and generics more competitive.

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## V. Key Development Issues

Previous clinical development of ABT-594 and pre-clinical development of A-429202 indicate neuronal nicotinic receptor (NNR) agonists may be beneficial in the treatment of pain. The Transition Team has evaluated the data gathered from ABT-594 studies and identified the following issues for consideration in the review of A-429202. These comments are based upon the assumption that the clinical profile of A-429202 will exhibit similar efficacy, but substantially reduced potential to evoke emesis vs. ABT-594. The following key issues must be addressed to ensure successful development of A-429202.

- Preclinical pain models have accurately predicted the plasma concentration necessary to achieve clinical efficacy in neuropathic pain with ABT-594. Assuming these predictions will hold true for A-429202, it will be possible to set specific plasma level targets in Phase I studies and determine whether an acceptable incidence of adverse events is associated with those plasma levels.
- Clinical experience with ABT-594 suggests that the rate of rise to a given plasma level may be an important determinant of the acute (single dose) tolerability of this drug. Although other factors than just rate of rise may have contributed (such as taste, esophageal absorption), very significant differences were seen in the tolerability of aqueous solution dosing (powder in bottle) vs. either soft elastic gelcap (SEC) or hard gelatin capsule (HGC) formulations. With A-429202, it will be necessary to carefully evaluate not only the tolerability of a given plasma level, but also how using different formulations to vary  $t_{max}$  affects tolerability. The Transition Team believes that this will be best accomplished by initiating studies with a parenteral and a capsule formulation, and avoiding solution dosing.
- The clearance and half-life of A-429202 in human must be appropriate to support BID dosing. More frequent dosing would have a significant negative impact on the commercial value of this compound.
- The metabolism and elimination of A-429202 in renally impaired patients must be established. A-429202 is largely metabolized by the CYP2D6 isoform. Five to eight percent of the general population is 2D6 deficient. The potential effects this will have on drug clearance in population subsets must be carefully evaluated.
- The onset and time to maximum concentration of A-429202 may not be rapid enough to provide acceptable analgesia for acute nociceptive pain. If delayed  $t_{max}$  is considered sub-optimal for acute pain, clinical evaluation of A-429202 will focus on chronic pain models, such as neuropathic pain.
- ABT-594 was evaluated in a model of acute nociceptive pain (molar extraction). While a significant effect was demonstrated, the magnitude of the effect was modest. The delayed  $t_{max}$  and lack of inhibition of prostaglandin function likely contributed to the modest efficacy. A-429202 should only be evaluated in this model if it exhibits a significantly shorter  $t_{max}$  than ABT-594.
- As a class, analgesics are subject to intense scrutiny with respect to abuse liability. The NNR mechanism of action of A-429202 will likely add to that level of scrutiny. Early in the development program, it will be necessary to evaluate the abuse liability potential of A-429202.

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## VI. Scientific Logic

### A. Background

Nicotinic acetylcholine receptors belong to a family of ligand-gated ion channels that are found in abundance at the neuromuscular junction, and are widely distributed throughout the central and peripheral nervous systems. They are comprised of five subunit proteins that combine to form a cation permeable pore at the cell surface. In neuronal tissues, multiple NNR subtypes may be assembled from a diverse array of subunits ( $\alpha 2$ - $\alpha 10$ ;  $\beta 2$ - $\beta 4$ ) and their specific pharmacology is directly influenced by their particular subunit composition. A vast array of potentially beneficial effects and toxicities has been associated with activation of NNRs. Disease targets for NNR modulators have included Parkinson's disease, Alzheimer's and associated dementias, ulcerative colitis, Tourette's syndrome, schizophrenia, depression, attention deficit hyperactivity disorder, smoking cessation and chronic pain. Adverse effects of NNR activation include cardiovascular and GI effects, addiction, seizures and respiratory effects. The current evidence strongly supports the concept that appropriate targeting of specific NNR subtypes can separate the beneficial and adverse effects.

NNR activation is a validated approach to the treatment of pain, supported by receptor knockout studies, antisense studies, demonstration of analgesic efficacy across a wide range of structurally diverse small molecules, and clinical data from ABT-594. The concept that NNR activation can produce analgesia can be traced back to the observation by Davis that nicotine was efficacious in a cat model of visceral pain<sup>9</sup>. The analgesic effects of nicotine are modest and of short duration, and occur at doses where cardiovascular and CNS-related side effects are significant. Consequently, this observation was largely ignored for decades until the resurgence in interest brought about by the discovery of the profound analgesic properties of the frog-derived toxin epibatidine<sup>10</sup>. Although epibatidine exhibits potent antinociceptive effects across a variety of rodent pain models, these effects are accompanied by significant hypothermia, ataxia, cardiovascular, and respiratory effects. In non-rodent models (dog, ferret) both nicotine and epibatidine produce significant nausea and vomiting within their therapeutic range. Both nicotine and epibatidine are non-selective activators of all known subtypes of NNRs and are also active at the neuromuscular junction ( $\alpha 1\beta 5$ ) receptor. Thus, the basis of the Abbott program has been to identify agents that selectively activate the NNR subtypes responsible for the analgesic properties of this pharmacological class.

### B. Drug Target

#### 1. NNR Subtypes Involved in Antinociception

Several lines of evidence from both knockout and antisense studies provide strong support for the involvement of the  $\alpha 4\beta 2$  subtype in NNR-mediated antinociception. Marubio et al.<sup>11</sup> have demonstrated that mice lacking either the  $\alpha 4$  or  $\beta 2$  NNR subunit exhibit a markedly attenuated antinociceptive response to nicotine (Figure 7) and epibatidine (data not shown), indicating that both subunits are involved in the NNR-mediated antinociception. Significant differences were seen between the hot plate model (a model of supraspinally mediated nociception) and the tail flick test (a model driven largely by spinal reflex). Consistent with this finding, patch clamp recording from 5-HT containing neurons in the raphe

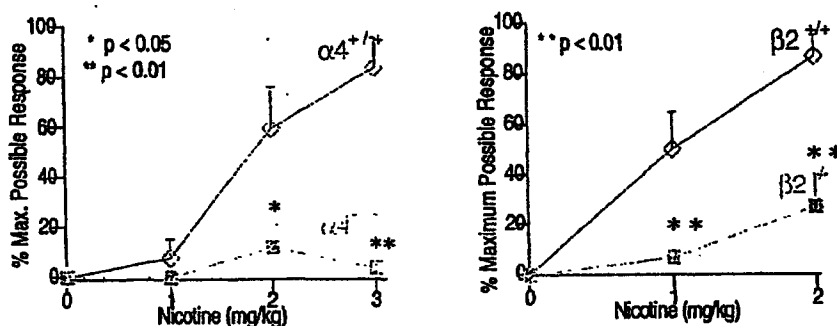


Figure 7. Antinociceptive Effects of Nicotine in Knockout Mice Lacking Either the  $\alpha 4$  or  $\beta 2$  NNR subunits in the Mouse Hot Plate Model of Acute Nociceptive Pain ( $\alpha 4^{+/-}$  refers to knockout mouse,  $\alpha 4^{+/+}$  to wildtype;  $\beta 2^{+/-}$  refers to knockout mouse,  $\beta 2^{+/+}$  to wildtype).

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magnus (a brainstem region implicated in the activation of descending inhibitory pain pathways) showed a loss of nicotine-induced currents in the  $\alpha 4$  and  $\beta 2$  null mutant mice, whereas recordings from neurons in the superficial lamina of the dorsal horn showed no change in nicotine-elicited augmentation of postsynaptic currents.

Antisense studies from our laboratories (Bitner, et al.<sup>12</sup>) in the rat also strongly support the role of the  $\alpha 4$  subunit in NNR-mediated antinociception. Continuous i.c.v. infusion for 7 days of an antisense oligonucleotide targeting the region of the start codon for the  $\alpha 4$  subunit, but not a missense oligo, decreased both  $\alpha 4$ -immunostaining in the brainstem and the antinociceptive effects of a prototypical NNR agonist A-85380 in the hotbox test of acute thermal pain (Figure 8). These data are consistent with the data from  $\alpha 4$  and  $\beta 2$  knockout animals, both with respect to involvement of the  $\alpha 4$  subunit (and by inference the  $\alpha 4\beta 2$  subtype) and the involvement of supraspinal descending inhibitory circuitry.

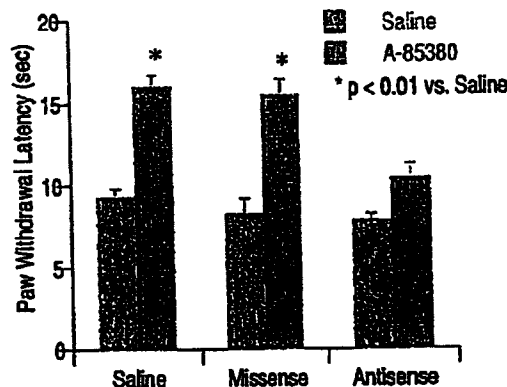


Figure 8. Antisense Knockdown of  $\alpha 4$  NNR Subunit in Rat Model of Nociception.

## 2. Site of Action

A strong body of evidence supporting a predominantly supraspinal site of action for NNRs in the activation of descending serotonergic and adrenergic pain inhibitory circuitry has been well documented (see Rueter, et al.<sup>13</sup>, Bitner, et al.<sup>14</sup>). These findings were almost exclusively derived from studies in which blockade of an acute thermal stimulus was being used as the behavioral endpoint. As these findings have been extended into additional models of persistent nociceptive pain (formalin model) and neuropathic pain (Chung model), it has become clear that additional sites of action for NNRs likely exist. Recent studies from our laboratory have implicated both central and peripheral sites of action of NNRs in neuropathic pain models. Peripheral sites have been localized to the dorsal root ganglia (DRG) cell bodies, and evidence exists for phenotypic changes in NNR receptor expression and subtype composition at the level of the DRG. Current evidence continues to implicate the  $\alpha 4\beta 2$  NNR subtype as being of critical importance at these peripheral sites as well as at supraspinal sites.

## 3. NNR Subtypes Correlated to Adverse Events

Although the evidence for the involvement of the  $\alpha 4$  and  $\beta 2$  subunits in the analgesic properties of NNR agonists is well documented, the role of other NNR subunits (particularly  $\alpha 3$ ,  $\beta 4$ , and  $\alpha 7$ ) is less well understood. Acute nicotine administration increases heart rate, myocardial contractility and blood pressure, and these effects are attributed to activation of nicotinic receptors localized on peripheral postganglionic sympathetic nerve fibers. The predominant NNR subtype of the sympathetic ganglia is  $\alpha 3\beta 4$ , and this subtype mediates the systemic release of norepinephrine. From knockout studies, mice lacking the  $\alpha 3$  gene exhibited extreme bladder enlargement and widely dilated ocular pupils that were unresponsive to light, confirming the significance of this subunit in the peripheral autonomic nervous system. The role of the  $\alpha 3$  subunit and  $\alpha 3\beta 4$  subtype in the mediation of emesis is less well established, and is based largely on correlation studies with subtype-selective agonists. Several key tool compounds have been identified that exhibit high selectivity for the  $\alpha 3\beta 4$  over  $\alpha 4\beta 2$  subtype. These compounds have exhibited significant emesis liability without exhibiting any significant effects in pain models.

## 4. Receptor Target Profile

The working hypothesis behind the identification of A-429202 is that an improved tolerability profile can be achieved by improving the selectivity for the  $\alpha 4\beta 2$  NNR subtype over the  $\alpha 3\beta 4$  subtype, and that efficacy can be retained in a compound exhibiting an improved selectivity profile. Broad-spectrum analgesic efficacy may require activation of both CNS and peripheral  $\alpha 4\beta 2$  NNRs.

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### C. Abbott Approaches and Advances—Clinical Experience with ABT-594

ABT-594 was a first-generation NNR agonist for the treatment of pain, and the first compound from this pharmacological class ever evaluated clinically as a potential analgesic agent. At the level of NNR subtype selectivity, ABT-594 is highly selective for the  $\alpha 4\beta 2$  subtype over the  $\alpha 1\beta\gamma\delta$  (muscle receptor) and the  $\alpha 7$  subtypes. It is, however, nearly equipotent at the  $\alpha 4\beta 2$  and  $\alpha 3\beta 4$  subtypes. In preclinical pain models, ABT-594 exhibited analgesic efficacy in models of nociceptive and neuropathic pain comparable to morphine, exhibited a significantly lower propensity to develop tolerance to analgesic effects relative to morphine, and was devoid of the sedating and constipating effects of morphine.

The preclinical profile of analgesic efficacy has been validated clinically. ABT-594 has exhibited clinical efficacy in the treatment of acute nociceptive, chronic nociceptive and chronic neuropathic pain. In the first Phase II trial, a single-dose oral solution of ABT-594 (25, 50, 75, and 100  $\mu\text{g}$ ) was compared to placebo and ibuprofen (400 mg) in a post-surgical dental pain model. A categorical 0 to 4 point scale was used where 0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete pain relief. This model is best suited to detection of analgesic efficacy for NSAIDs (and in particular ibuprofen), favoring rapid onset and suppression of injury-induced prostaglandin formation. The 100  $\mu\text{g}$  single dose of ABT-594 was demonstrated to be an effective analgesic dose, with onset of action of approximately 2 hours (Figure 9). The slow onset of action was consistent with the delayed  $t_{\text{max}}$  ( $2.4 \pm 2.0$  h). With rescue medication permitted after 90 minutes, the full potential of this drug to produce analgesia may have been compromised. At the 100  $\mu\text{g}$  dose, adverse events significantly different from placebo were dizziness (24% vs. 4% for placebo), nausea (32% vs. 12% for placebo), and vomiting (20% vs. 2% for placebo). From this study, it was concluded that ABT-594 was not an appropriate drug for continued evaluation in the treatment of acute pain.

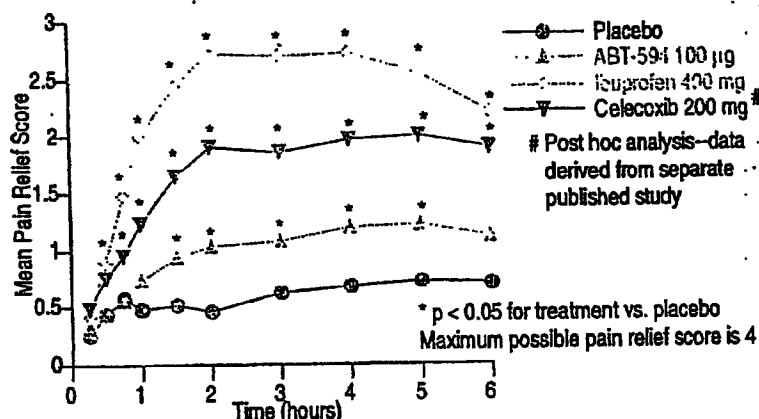


Figure 9. Evaluation of ABT-594 in a post-surgical model of dental pain.

Based on these findings, two additional Phase II trials in pain associated with osteoarthritis and neuropathic pain were initiated. A soft elastic capsule (SEC) formulation was used for these two trials. Bioequivalence studies established that 75  $\mu\text{g}$  BID administration of the SEC formulation produced higher  $C_{\text{max}}$  values at steady-state than were achieved with a single solution dose of 100  $\mu\text{g}$  (0.74 ng/mL vs. 0.65 ng/mL). Based on the limited tolerability of the 100  $\mu\text{g}$  solution dosing, 75  $\mu\text{g}$  BID was selected as the top dose for both of these Phase II studies. However, adverse events from these two trials were substantially lower than anticipated (Table 7).

Table 7. Adverse events associated with solution and SEC dosing formulations of ABT-594.

Event	Molar Extraction		OA and Neuropathic Pain	
	100 $\mu\text{g}$ x 1 Solution (n=50)	Placebo	75 $\mu\text{g}$ BID SEC (n=96)	Placebo
Nausea	32%	12%	15%	3%
Vomiting	20%	2%	5%	0%
Dizziness	24%	4%	7%	5%

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In the osteoarthritis trial, ABT-594 (25, 50, and 75 µg BID, for 3 weeks) was compared to placebo and ibuprofen (400 mg TID). Efficacy was evaluated using the 500-point WOMAC pain sub-scale, where patients were asked to evaluate their level of pain associated with walking on flat surfaces, going up and down stairs, etc. Baseline pain scores for the 75 µg ABT-594 group was 305 (i.e., the maximum change from baseline would be 305). Both 75 µg ABT-594 and 400 mg ibuprofen produced an approximately 100-point change in pain ratings. Although statistically significant differences were not detected, ABT-594 75 µg BID was numerically better than placebo as measured by all WOMAC pain subscale scores and was similar to ibuprofen (Figure 10).

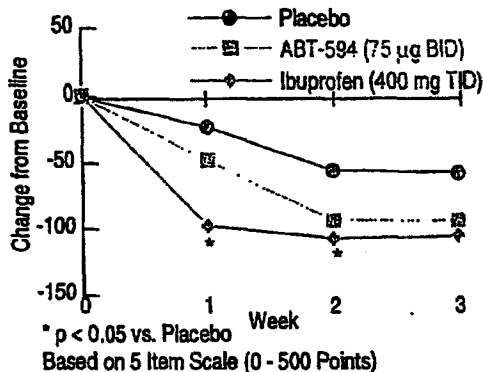


Figure 10. Efficacy of ABT-594 (75 µg, BID) in the treatment of pain associated with osteoarthritis.

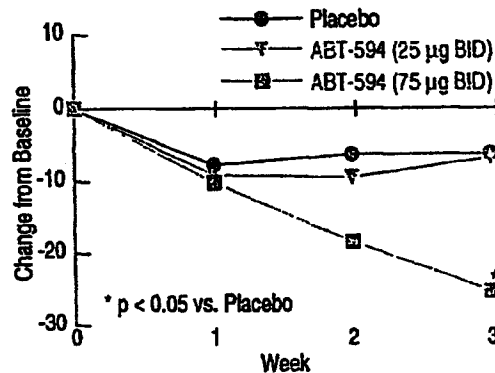


Figure 11. Efficacy of ABT-594 (75 µg, BID) in the treatment of painful diabetic neuropathy.

The neuropathic pain trial compared ABT-594 (25 and 75 µg bid, for 3 weeks) to placebo. A 10-item, 100-point neuropathic pain scale was used for this analysis, in which patients were asked to evaluate their pain, querying various aspects of their pain most frequently associated with neuropathic pain (i.e., sharpness, itching, numbness, etc.). The baseline (pre-treatment) score for the 75 µg ABT-594 group was 52 (maximum achievable change). Again, although statistically significant differences were not detected in the whole population (50% diabetic neuropathy, 50% idiopathic), ABT-594 75 µg BID was numerically better than placebo as measured by the Total Neuropathic Pain Scale. A significant effect of ABT-594 was revealed in a post-hoc subset analysis of patients with diabetic polyneuropathy, which exhibited a 27-point change (50%) from baseline scores (Figure 11).

Based on the positive signal among diabetics in the neuropathic pain trial and the better-than-expected tolerability observed in this trial, a second trial targeting painful diabetic neuropathy using doses of 150, 225, and 300 µg BID was initiated. All three dosing groups exhibited statistically significant pain relief as measured by the primary efficacy variable (reduction in daily pain), but analysis based on intent to treat (ITT) failed to demonstrate a dose-related effect. Among completers (keeping in mind the caveat that dropout rates for the 150, 225, and 300 µg BID groups were 40%, 58% and 75% vs. 26% for placebo group) dose-dependent improvement ranging from 38% to 48% (vs. 18% for placebo) was achieved (Figure 12).

An across-study comparison of these results to the published studies on gabapentin and pregabalin suggest that the level of efficacy achieved in this study is at least as great as that reported for these benchmark compounds (Figure 13).

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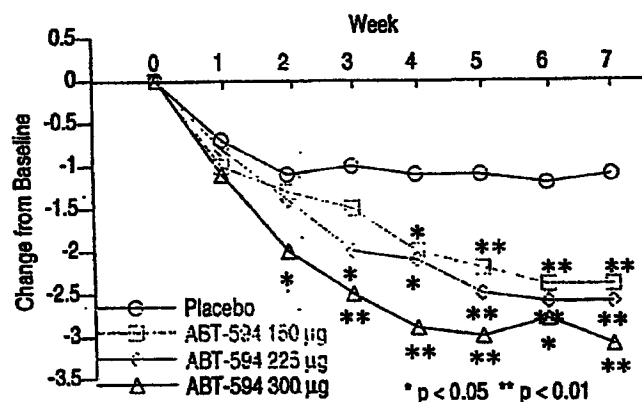


Figure 12. Evaluation of ABT-594 (150, 225, and 300 µg, BID) in the treatment of painful diabetic neuropathy (ABT-594 analysis based on completers for each dosing group).

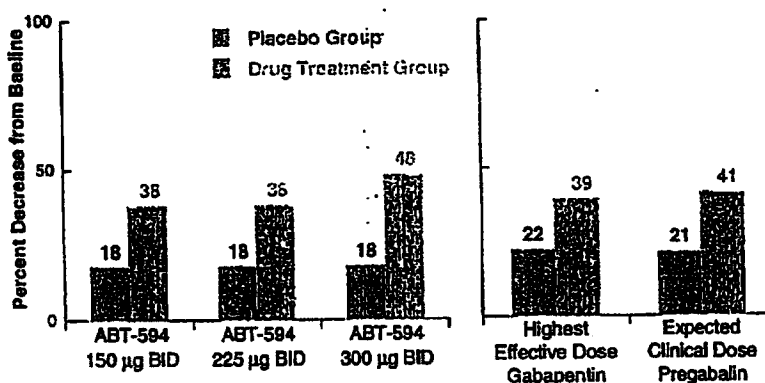


Figure 13. Percent Change from Baseline in Comparison to Gabapentin and Pregabalin.

The levels of adverse events were, however, substantial and dose-related. Adverse event related discontinuation rates of 28%, 46% and 66% were realized for the 150, 225 and 300 µg groups, respectively. Adverse events recorded at levels above placebo are reported in Table 8. The high dropout rate was driven almost exclusively by adverse events and not a lack of efficacy. In the 300 µg dose group, adverse events were responsible for 66% of dropouts vs. 9% for the placebo group; lack of efficacy produced dropouts in 7% of the ABT-594 300 µg group vs. 9% for placebo.

Table 8. Adverse Events associated with ABT-594 at 150, 225, and 300 µg, BID.

Event	Placebo (n = 65)	ABT-594 150 µg BID (n = 65)	ABT-594 225 µg BID (n = 69)	ABT-594 300 µg BID (n = 67)
Nausea	11%	34%	43%	46%
Vomiting	3%	15%	25%	21%
Dizziness	5%	17%	35%	28%
Abnormal Dreams	0%	22%	22%	18%
Asthenia	2%	6%	16%	19%

By mapping plasma levels from the dosing groups examined to plasma levels required in preclinical studies to achieve a given level of efficacy, this analysis suggests that the NNR pharmacology may be able to reach greater efficacy than was observed during this clinical experiment (Figure 14). The top dosing group (300 µg, BID) produced a steady state  $C_{max}$  of 2.84 ng/mL,

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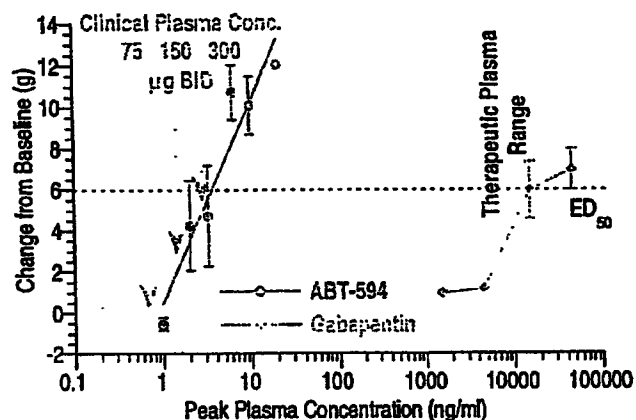
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which in preclinical experiments in the Chung neuropathic pain model was sufficient to produce approximately 40% of maximally achievable efficacy. The dose-dependent increase in efficacy observed in this trial, plus the lack of statistically significant efficacy (using the primary end point) observed from the previous trial (dosing at 75 µg, BID) are predicted by this plasma level analysis. The model also accurately predicts the plasma levels required by gabapentin to produce clinically meaningful efficacy. These results support the conclusion that given a compound with expanded therapeutic index, at a minimum it should be possible to achieve comparable efficacy to gabapentin with a substantially benign side effect profile, and it may be possible to attain greater efficacy than has been observed thus far with ABT-594.



**Figure 14. Correlation of Preclinical Plasma Levels in Chung Model of Neuropathic Pain to Clinical Results**

A-429202 meets the criteria defined by the clinical experience with ABT-594 (see following sections). Preclinical models suggest that efficacy comparable to the 300 µg BID dosing group will be achieved with A-429202 at plasma levels in the range of 10 to 30 ng/mL. These values are below the plasma levels required to elicit emesis in the ferret model.

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## VII. Target Product Profile

In clinical studies, ABT-594 demonstrated efficacy in Phase II neuropathic pain trials, and a positive trend toward efficacy was seen in a low-dose Phase IIa trial in pain associated with osteoarthritis. However, ABT-594 did not display an acceptable tolerability profile with respect to nausea and emesis. The efficacy of ABT-594 suggests that A-429202 should be evaluated in clinical studies utilizing several pain models including both neuropathic and nociceptive pain. Neuropathic pain should be pursued as the lead indication, while early clinical studies in selected nociceptive pain models are crucial to help us determine the potential of A-429202 in this type of pain.

Table 9. Opportunity Comparison – Neuropathic Pain and Nociceptive Pain.

	Neuropathic Pain	Nociceptive Pain
Pros	<ul style="list-style-type: none"> <li>• Greater unmet need.</li> <li>• NNR concept in the relief of neuropathic pain has been validated by ABT-594.</li> <li>• Relatively cheaper and shorter than chronic nociceptive pain models.</li> <li>• Relatively lower hurdles in technical success and competition.</li> <li>• Specialty sell with lower SG&amp;A.</li> <li>• With Neurontin likely to get an approval, awareness building and market development will likely expand the treatment market dramatically.</li> </ul>	<ul style="list-style-type: none"> <li>• Huge patient population.</li> <li>• High unmet need in moderate to severe chronic pain segments.</li> </ul>
Cons	<ul style="list-style-type: none"> <li>• Smaller patient population than nociceptive pain.</li> <li>• Regulatory pathway yet to be fully defined.</li> </ul>	<ul style="list-style-type: none"> <li>• NNR's efficacy in the relief of nociceptive pain needs to be further defined in clinical studies.</li> <li>• High hurdles to demonstrate clinical advantage over COX-2's, but less so for opioids.</li> <li>• A highly competitive market: major brands, generics, etc.</li> <li>• Competitive SG&amp;A spend.</li> </ul>
Overall	<ul style="list-style-type: none"> <li>• Significant unmet need, lower technical hurdles and a rapidly growing market.</li> </ul>	<ul style="list-style-type: none"> <li>• Higher technical hurdles; highly competitive market; but huge population base.</li> </ul>

### A. Neuropathic Pain

A strategic priority for A-429202 is to demonstrate its clinical potential in neuropathic pain. Based upon market research on ABT-594, two product profiles are anticipated to achieve 1<sup>st</sup> line choice (See Table 10).

If either scenario can be delivered, the primary market research on ABT-594 (June, 2001) indicates that it would achieve 1<sup>st</sup> line choice, and the estimated global sales potential of this compound would be approximately \$1 billion. A scenario that would deliver 1<sup>st</sup>/2<sup>nd</sup> line choice, with an estimated global sales potential of \$670 million, was also considered commercially viable with ABT-594, in which case similar efficacy to Neurontin and low emesis and nausea need to be achieved. These projections are based on ABT-594 and the projected timeline for its approval, and therefore do not take into account the later entry of a new compound and additional competitive compounds that may be marketed in the interim. The neuropathic pain market will likely become increasingly competitive with the inroad by generic gabapentin and the introduction of prebalign (likely after 2002/2003). The target positioning for A-429202 is to achieve 1<sup>st</sup> line choice in a broad range of neuropathic pain stages.

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Table 10. Target Product Profile for Neuropathic Pain.

*A-429202 potential positioning in neuropathic pain: to achieve 1<sup>st</sup> line choice in a broad range of neuropathic pain stages.*

Product Attribute	Neurontin	Target Profile	
		Scenario 1	Scenario 2
Efficacy	2.1 to 2.5 absolute point reduction*	2.5 to 3.0 absolute point reduction	3.0 to 3.5 absolute point reduction
Vomiting	0%	3%	10%
Nausea	8%	10%	20%
Discontinuation rate due to adverse events	13%	13%	13%
Dizziness	24%	10%	24%
Abnormal Dreams	0%	10%	10%
Use of anti-emetics	No	No	No
Responder Rate	60%	Similar to Neurontin	
Duration for titration	4 weeks	Similar to Neurontin	
Dosing	TID	BID	
Addiction potential	Non-addicting	Non-addictive; doesn't re-initiate ex-smokers' craving	
DEA scheduling	Not scheduled	Not scheduled	

Source: Neurontin data from Neurontin studies on diabetic neuropathy and post-herpetic neuralgia.

\* 11-point Likert weekly average of daily Pain Rating Scale.

## B. Nociceptive Pain

The strong efficacy signals of ABT-594 and A-429202 in preclinical nociceptive pain models need to be more definitively demonstrated in clinical studies. The unmet need in the moderate to severe nociceptive pain market is huge, with 60 million people in the US and over 150 million worldwide desiring new pain medications that can offer opioid-like efficacy without the opioid-like side effect profile. However, the size of A-429202's potential in nociceptive pain treatment can vary from unattractive to highly attractive, likely determined by:

- Its level of efficacy in nociceptive pain: an NSAID-like efficacy will likely force A-429202 to compete in the NSAIDs/COX-2's space, which is well served and in which A-429202 is not likely to offer any clinical advantage. However, opioid-like efficacy may allow A-429202 to penetrate the broader moderate to severe pain market.
- The need/or no need for titration: the potential necessity for titration will likely limit A-429202's opportunity to the chronic persistent pain segment only.
- Its onset of action: together with the necessity for titration, onset of action will determine how much A-429202 can penetrate the acute pain segment.

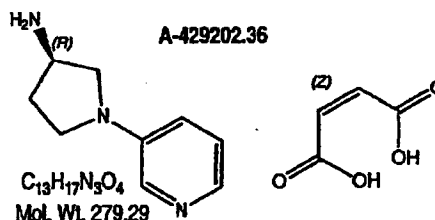
It is crucial for Abbott to conduct early clinical studies in selected nociceptive pain models to evaluate A-429202's true properties around the above three key attributes so that a Go/No Go decision can be made with regard to the development in nociceptive pain.

## VIII. Physical and Chemical Characterization

### A. Physiochemical Properties

#### 1. Structure and Solid State Properties

The melting point of the crystalline free base is exceedingly low. The maleic acid salt selected in collaboration with Process Chemistry group, was found to be crystalline having a melting point of 180°C with decomposition. The moisture uptake profiles in Figure 15 show that two of the three lots of this salt were non-



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hygroscopic over the RH range of 0 to 90% at 40°C. The hygroscopic behavior of lot number 74198-150 was attributed to the presence of an impurity. Since it is possible to isolate the maleate salt without this impurity, A-429202.36 is determined to have acceptable physicochemical properties.

## 2. $pK_a$ , Lipophilicity and Solubility

The  $pK_a$ 's of the compound were determined to be  $6.1 \pm 0.01$  and  $8.8 \pm 0.02$  by potentiometric titration. Based on the  $pK_a$  values the compound will be ionized over the relevant physiological pH range. The pH-log D profile (Figure 16) was also generated by potentiometric titration and the log P value indicates that the compound is not prohibitively hydrophilic over the range of intestinal pH values. The solubility of the compound determined between pH values of 5.5 to 12 was greater than 14 mg/mL and the solubility is expected to increase with decreasing pH values. The compound is highly soluble. The intrinsic dissolution rate of the maleate salt at pH 6.8 is 27 mg/minute/cm<sup>2</sup>, which is exceedingly rapid.

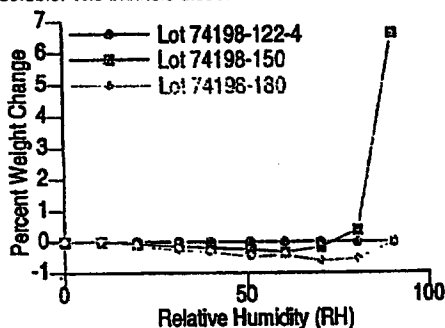


Figure 15. Moisture Uptake Profile of different lots of A-429202.36.

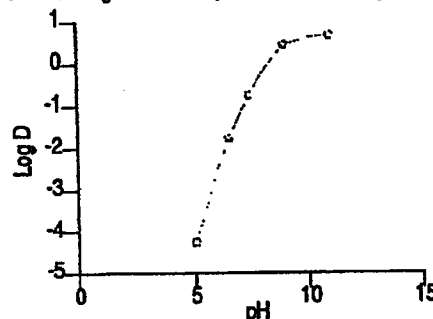


Figure 16. The pH Log D profile of A-429202.

## 3. Stability

The results from solution photostability studies over the pH range of 1 to 12 are summarized in Table 11. Since the extent of degradation at pH 7.4 (50mM phosphate) was higher than at pH 1, 4.5 or 12, the pH 7.4 studies were repeated using both a 25mM phosphate buffer and TRIS buffer. The results indicate that in the presence of phosphate buffer A-429202.36 degrades at a faster rate. In summary A-429202.36 solutions degraded when exposed to UV light but the solutions were stable when exposed to visible light. In the solid state A-429202.36 is photostable.

Table 11. Photostability of A-429202.36 at 20 °C.

Concentration (µg/mL)	Exposed to UV & Visible Light		Exposed to Visible Light	
	Control	Sample	Control	Sample
pH 1	29.96 ± 0.94	28.12 ± 0.74 <sup>P</sup>	29.68 ± 0.77	28.87 ± 0.87
pH 4.5	31.12 ± 1.04	27.58 ± 0.93 <sup>P</sup>	31.73 ± 0.78	31.28 ± 0.66
pH 7.4 (50mM phosphate)	36.52 ± 0.21	19.86 ± 2.08 <sup>P</sup>	36.01 ± 0.47	36.17 ± 1.06
pH 7.4 (25mM phosphate)	30.51 ± 0.39	22.32 ± 0.08 <sup>P</sup>	-	-
pH 7.4 (50mM TRIS)	33.31 ± 0.2	29.6 ± 0.1 <sup>P</sup>	-	-
pH 12	35.72 ± 0.75	30.21 ± 0.71 <sup>P</sup>	35.19 ± 0.74	35.20 ± 0.14
Solid: Percent Recovered	106 ± 4.03	101 ± 1.62	101 ± 2.43	104 ± 0.48

<sup>P</sup>=chromatogram shows the presence of degradation peaks

Solutions at pH values 1, 4.5, 7.4 and 12 were stored in the dark at temperatures 60, 75 and 90 °C. The pH 7.4 studies were performed using 50mM phosphate buffer and although these solutions were found to be least stable, as discussed above, this lack of stability could be due to the use of phosphate buffer. The pH 1, 4.5 and 12 solutions when stored at 90 °C for 15 days showed ~10% loss in potency; therefore, protected from light these solutions are stable. The solid-state stability studies at 40°C/75%RH protected from light were initiated with lot number 74198-150 but the samples deliquesced after 3 weeks. As discussed above, this phenomenon was attributed to the presence of an impurity in this lot. Solid-state stability studies have been re-initiated.

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## B. First in Man Formulation/Commercial Formulation

Assuming that A-429202.36 is stable in the solid state, and given that the projected oral dose is 10 to 15 mg, a simple formulation containing the drug and excipient in capsule could be used for First in Man studies. Based on physicochemical properties (pH-solubility profile, intrinsic dissolution rate, etc.) it is concluded that the commercial development of an oral solid dosage form should be feasible. The pH of maximum stability needs to be determined for the evaluation of commercial solution formulation. Based on high solubility and acceptable stability, development of an IV formulation for first in man studies should also be feasible.

## IX. Patent Status

A U.S. patent application claiming A-429202 was filed May 21, 1999 in the United States Patent and Trademark Office. The application was foreign filed worldwide on May 15, 2000, and published as WO 00/71534 A1 on November 30, 2000. The projected patent protection in the U.S. extends to May 21, 2020, while ex-U.S. coverage extends to May 15, 2020. No office actions have been received to date.

## X. Process Chemistry

### A. Synthesis

The current synthesis is designed around the Buchwald-Hartwig Pd-catalyzed amination reaction, which accomplishes the key N-aryl connection between the pyridine and the aminopyrrolidine. For the initial clinical campaign, the starting material is 3-(R)-amino-1-benzylpyrrolidine, which is commercially available. A salt screen has been completed, and after collaboration with the pharmaceuticals group, the maleate salt has been identified as the lead candidate.

As shown in Figure 17, the route proceeds in 4 steps, with an overall yield from 3-(R)-amino-1-benzylpyrrolidine of 55%. The 3-(R)-N-Boc-aminopyrrolidine (1) is synthesized in two steps, and 86% yield. Reaction of 1 with 3-bromopyridine, under palladium catalysis conditions, leads to the Boc-protected product (2). Deprotection is achieved with aqueous hydrochloric acid and subsequent addition of maleic acid provides A-429202.36.

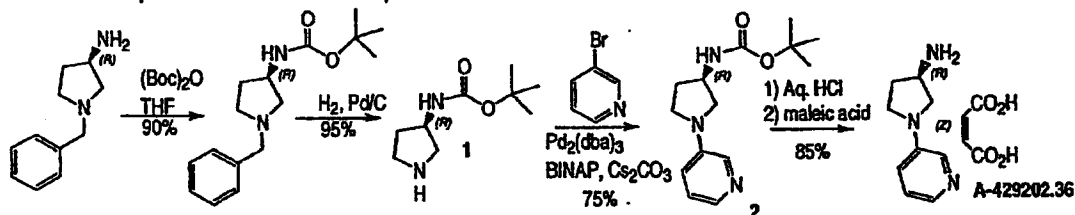


Figure 17. Current synthetic route for the preparation of A-429202.

The current route provides an efficient method to make A-429202.36, however, several patents (to M.I.T and Yale University) have recently been issued that cover much of the Buchwald-Hartwig chemistry. In addition, the cost of palladium catalyst and residual palladium removal makes this chemistry less attractive for long-term needs. Alternate synthetic strategies will be explored for post-Phase I deliveries.

### B. Cost of Goods

It is estimated that the planned campaign to deliver ca. 1.7 Kg of active pharmaceutical ingredient (API) will meet the needs of toxicology and Phase I, at a total cost of approximately \$378,000 (details below). The kilo facility will be used to prepare intermediate 2, however due to limited potent drug handling capability the delivery date of API will be dependent on facility availability. With the current schedule and project prioritization, delivery of API can be expected 2-3 months after DDC approval.

Total	FTE's Chem.	FTE's Analytical	Materials
\$378K	1.0 \$281.7K	0.25 \$45.6K	\$50K

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## XI. *In Vitro* Pharmacology

A-429202 exhibits high affinity ( $K_i = 0.187$  nM) for and shows full functional efficacy at the  $\alpha 4\beta 2$  NNR ( $EC_{50} = 0.18$   $\mu$ M), and exhibits approximately 10-fold greater selectivity for  $\alpha 4\beta 2$  over  $\alpha 3\beta 4$  receptors than ABT-594. A-429202 exhibits significantly enhanced radioligand binding selectivity for the  $\alpha 4\beta 2$  NNR subtype relative to  $\alpha 7$ , and unlike ABT-594, which is a full agonist at the  $\alpha 7$  site, A-429202 is functionally inactive at the  $\alpha 7$  receptor. A-429202 exhibits a high degree of selectivity for the  $\alpha 4\beta 2$  NNR receptor vs. a panel of 78 receptors, transporters and ion channels.

### A. Receptor Binding Studies

A-429202 displays high affinity competitive binding to the [ $^3$ H] (-)-cytisine binding site in rat brain, which represents binding to a desensitized form of the native rat  $\alpha 4\beta 2$  NNR, and is also considered to be the high affinity (-)-nicotine binding site in brain.<sup>15</sup> The  $K_i$  value for A-429202 is  $0.187 \pm 0.004$  nM ( $n=3$ ), 5-fold less potent than ABT-594, which displays a  $K_i$  of  $0.037 \pm 0.008$  nM ( $n=11$ ). In contrast, A-429202 shows very weak affinity for the  $\alpha$ -BTX binding site in rat cortical membranes which represents binding to the  $\alpha 7$  NNR subtype<sup>16</sup>, exhibiting a  $K_i$  of  $11.9 \pm 2.4$   $\mu$ M ( $n=3$ ), 64,000-fold greater than its  $K_i$  for the  $\alpha 4\beta 2$  NNR. ABT-594 has a  $K_i$  of  $0.61 \pm 0.14$   $\mu$ M ( $n=4$ ) at the  $\alpha$ -BTX binding site.

A-429202 shows very weak affinity for the human neuromuscular subtype,  $\alpha 1\beta \gamma \delta$ , expressed in native form in the TE671 human cell line, and represented by the  $\alpha$ -BTX binding site in these cells. A-429202 shows a  $K_i$  of  $2 \pm 0.5$   $\mu$ M ( $n=3$ ), which is approximately 11,000-fold greater than its  $K_i$  for the cytosine binding site, reflecting binding to  $\alpha 4\beta 2$  NNR. The  $K_i$  for ABT-594 in TE671  $\alpha$ -BTX competitive binding experiments is  $0.5 \pm 0.06$   $\mu$ M ( $n=3$ ).

Thus, like ABT-594, A-429202 shows much greater affinity for the heteromeric  $\alpha 4\beta 2$  neuronal nicotinic receptor subtype than it does for the homomeric  $\alpha 7$  NNR or the heteromeric neuromuscular nicotinic receptor  $\alpha 1\beta \gamma \delta$ .

### B. Functional Activity

#### 1. Modulation of Calcium Dynamics

a. *Human NNRs*: The effects of A-429202 on  $Ca^{2+}$  influx were assayed using FLIPR in four cell lines expressing different human recombinant NNR subtypes as well as in the human ganglionic-like neuroblastoma cell line IMR 32, which expresses a native  $\alpha 3$  containing NNR subtype.

A-429202 activates  $Ca^{2+}$  influx through the human  $\alpha 4\beta 2$  NNR subtype with an  $EC_{50}$  of  $182 \pm 27$  nM and a maximal intrinsic activity of 148% relative to 100  $\mu$ M (-)-nicotine ( $n=6$ ). The compound shows similar potency and efficacy at the human  $\alpha 4\beta 4$  subtype, demonstrating an  $EC_{50}$  of  $242 \pm 9$  nM and a maximal intrinsic activity of 110% relative to (-)-nicotine ( $n=6$ ). At the  $\alpha 3$  NNR subtypes, the potency of A-429202 was significantly less. In IMR cells and at the human recombinant  $\alpha 3\beta 4$  subtype A-429202 showed  $EC_{50}$  values of  $4.3 \pm 0.79$   $\mu$ M ( $n=5$ ) and  $1.8 \pm 0.09$   $\mu$ M ( $n=3$ ) with maximal intrinsic activities of 112% and 104% relative to (-)-nicotine, for IMR and human recombinant  $\alpha 3\beta 4$ , respectively. For the human  $\alpha 3\beta 2$  subtype A-429202 displayed an  $EC_{50}$  of  $10 \pm 0.69$   $\mu$ M ( $n=3$ ), and only 39% maximal intrinsic activity relative to (-)-nicotine. Thus, A-429202 is approximately 10-fold more potent at the  $\alpha 4\beta 2$  NNR, the subtype indicated in analgesic/antiallostatic behavior, than at the  $\alpha 3\beta 4$  subtype, believed to play a role in emetic and cardiovascular liabilities.

ABT-594 shows less selectivity for the  $\alpha 4\beta 2$  over the  $\alpha 3\beta 4$  NNR subtype. ABT-594 activates  $Ca^{2+}$  influx through the human  $\alpha 4\beta 2$  NNR subtype with an average  $EC_{50}$  of  $50 \pm 12$  nM ( $n=6$ ) and an average maximal intrinsic activity of 123%. At the human  $\alpha 4\beta 4$  subtype ABT-594 exhibits an  $EC_{50}$  of  $14 \pm 1$  nM ( $n=6$ ) and maximal intrinsic activity of 96%. At the human ganglionic-like,  $\alpha 3$  expressing, IMR cell line the  $EC_{50}$  for ABT-594 is  $148 \pm 25$  nM ( $n=6$ ), with a maximal intrinsic activity of 133%, and at the human recombinant  $\alpha 3\beta 4$  ABT-594 shows an  $EC_{50}$  of  $197 \pm 27$  nM ( $n=8$ ) and maximal activity of 159%. ABT-594 is also a full agonist, unlike A-429202, at the human  $\alpha 3\beta 2$  subtype, demonstrating an  $EC_{50}$  of  $2.68 \pm 0.79$   $\mu$ M ( $n=13$ ), and a maximal intrinsic activity of 110%. Thus A-429202 shows better selectivity for the  $\alpha 4$  over  $\alpha 3$  subtypes versus ABT-594. Figure 18 provides a graphical representation of the profiles for  $\alpha 4\beta 2$  and native  $\alpha 3\beta 4$  (IMR-32 cell line) for both A-429202 and ABT-594.

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b. *Non-Human NNRs*: The functions of A-429202 and ABT-594 were also measured at non-human NNRs. A-429202 also activates  $\text{Ca}^{2+}$  influx, measured using FLIPR, at ferret  $\alpha 4\beta 2$  NNRs in a stable cell line expressing this receptor. A-429202 demonstrates an  $\text{EC}_{50}$  of  $214 \pm 9 \text{ nM}$  ( $n=4$ ), with a maximal activity of 165% relative to (-) - nicotine in the F14 stable cell line. This value is very similar to its  $\text{EC}_{50}$  at the human receptor. ABT-594 shows an  $\text{EC}_{50}$  of  $26 \pm 8 \text{ nM}$  ( $n=4$ ), with a maximal activity of 202% in this cell line.

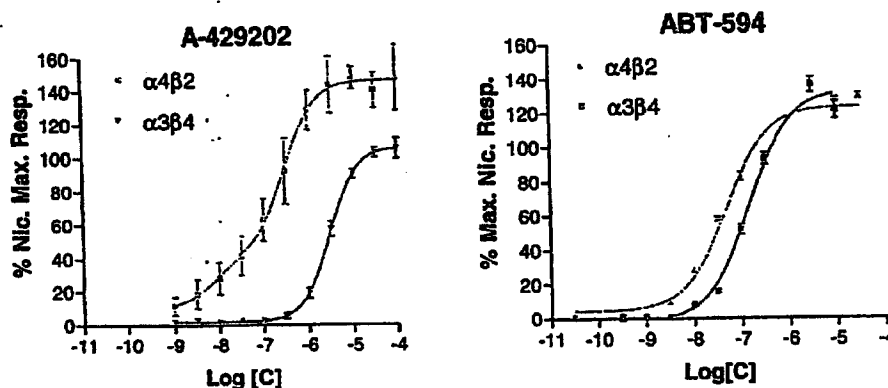


Figure 18.  $\text{Ca}^{2+}$  influx mediated by  $\alpha 4\beta 2$  or  $\alpha 3\beta 4$  NNRs assayed using FLIPR after addition of A-429202 or ABT-594.

## 2. Electrophysiology

The effect of A-429202 at the human  $\alpha 7$  receptor was functionally assessed by electrophysiology in *Xenopus* oocytes microinjected with human  $\alpha 7$  cRNA, and using POET (parallel oocyte electrophysiology tester system). A-429202 was essentially inactive at the human  $\alpha 7$  receptor, showing only 4% maximal activity at  $100 \mu\text{M}$  ( $n=2$ ). In contrast, ABT-594 demonstrates full agonist activity at the  $\alpha 7$  receptor, with an  $\text{EC}_{50}$  of  $7.98 \pm 0.71 \mu\text{M}$  ( $n=6$ ), and a maximal intrinsic activity of 130% relative to 10 mM acetylcholine. Thus, A-429202 also shows greater selectivity for the heteromeric  $\alpha 4$  receptors over the homomeric  $\alpha 7$  receptor, than ABT-594.

## 3. [ $^3\text{H}$ ]Dopamine Release

NNRs exhibit modulatory effects on a number of neurotransmitter systems including dopaminergic, serotonergic, noradrenergic, cholinergic, GABAergic and glutamatergic systems.<sup>17</sup> The effect of A-429202 on the release of dopamine was measured since there is significant evidence in the literature to suggest that dopamine release is mediated at least in part by the  $\alpha 4\beta 2$  receptor. [ $^3\text{H}$ ] dopamine release from rat striatal slices was measured in a 96-well format<sup>18</sup> and normalized to that evoked with  $100 \mu\text{M}$  nicotine (100%). A-429202 evoked the release of dopamine in this system with an  $\text{EC}_{50}$  of  $13 \pm 7 \text{ nM}$  ( $n=5$ ) and exhibited a maximal release of 157% relative to (-)-nicotine. This release was fully blocked by  $10 \mu\text{M}$  mecamylamine, an NNR selective antagonist (Figure 19). In comparison, ABT-594 evoked dopamine release with a similar potency demonstrating an  $\text{EC}_{50}$  of  $7 \pm 4.5 \text{ nM}$  ( $n=3$ ), and an average maximal release of 228% relative to (-)-nicotine. The effect was also blocked by mecamylamine. Additional studies to investigate the effects of A-429202 on other neurotransmitters (i.e. 5-HT, NE) involved in analgesia will be performed as part of the transition team activities.

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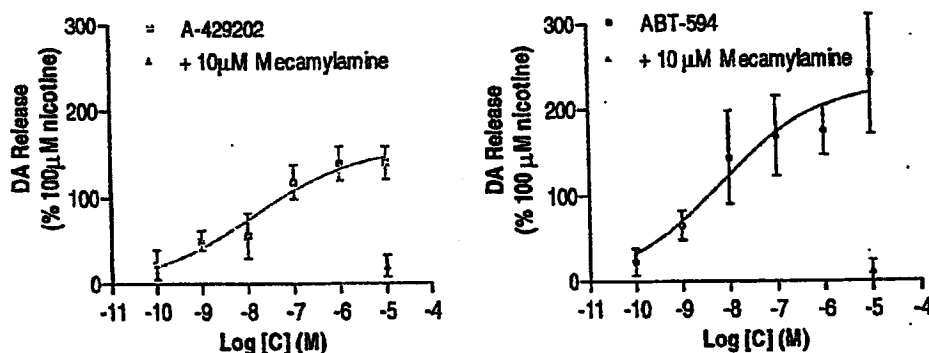


Figure 19. *In vitro* release of [<sup>3</sup>H] dopamine from rat striatal slices after addition of A-429202 or ABT-594.

Table 12 below summarizes the *in vitro* NNR effects of A-429202 and ABT-594.

Table 12. *In vitro* Properties of A-429202 and ABT-594 on NNR Mediated Effects

Assay	A-429202	ABT-594
<b>Radloliand Binding (K<sub>i</sub>, nM)</b>		
Rat α4β2	0.187 ± 0.004	0.037 ± 0.008
Rat α7	11,900 ± 2,400	610 ± 140
Human α1β1γδ	2,000 ± 500	500 ± 60
<b>Ion-Gating FLIPR (EC<sub>50</sub>, μM (intrinsic maximal efficacy vs. 100 μM nicotine))</b>		
Human α4β2	0.182 ± 0.027 (148%)	0.050 ± 0.012 (123%)
Human α4β4	0.242 ± 0.009 (110%)	0.014 ± 0.003 (96%)
Human α3β4	1.8 ± 0.09 (104%)	0.197 ± 0.027 (159%)
Human α3β2*	10 ± 0.69 (39%)	2.68 ± 0.79 (110%)
Human ganglionic-like - IMR 32 cells	4.3 ± 0.79 (112%)	0.148 ± 0.025 (133%)
Ferret α4β2	0.214 ± 0.009 (165%)	0.026 ± 0.008 (202%)
<b>Electrophysiology (EC<sub>50</sub>, μM (intrinsic maximal efficacy vs. 1 mM ACh (α4β2) or 10mM ACh (α7)))</b>		
Human α7	4% @ 100μM	7.98 ± 0.71 (130%)
<b>Neurotransmitter Release (EC<sub>50</sub>, μM (intrinsic maximal efficacy vs. 100 μM Nicotine))</b>		
Dopamine (from rat striatum)	0.013 ± 0.007 (157%)	0.007 ± 0.0045 (228%)

\* α3β2 responses were measured in the α3β2 (NeuroSearch) cell line for A-429202 and in the K414 cell line (Abbott Park) for ABT-594; both cell lines express the human receptor.

### C. Selectivity with Respect to Other Receptors

A-429202 exhibits a highly selective profile for NNRs, as demonstrated in results of binding data on 78 different receptors/transporters/ion channels. The majority of these receptors were assayed at Cerep (Cerep study report # 860191) and results are shown in Table 13 below. In this study the only potentially significant displacement of binding by A-429202 was to the μ opioid receptor, where the compound showed very modest affinity (63% at 10 μM). A K<sub>i</sub> value of 3.1 μM was subsequently determined for affinity of A-429202 to the μ-opioid receptor. This affinity does not appear to have functional significance, since A-429202-induced analgesia was not affected by pretreatment with an opioid receptor antagonist (see *In Vivo* Pharmacology Section).

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Table 13. Cerep Radioligand Binding Profile.

Receptor	% Inhibition	Receptor	% Inhibition
A1	<10%	M2	<10%
A2a	<10%	M3	<10%
$\alpha$ 1	<10%	M4	31%
$\alpha$ 2	<10%	M5	22%
$\beta$ 1	<10%	NK <sub>1</sub>	<10%
$\beta$ 2	11%	NK <sub>2</sub>	<10%
NE transporter	<10%	NK <sub>3</sub>	<10%
AT <sub>1</sub>	16%	Y1	17%
AT <sub>2</sub>	<10%	Y2	<10%
ANP	<10%	NT	<10%
BZD (central)	<10%	$\delta$	<10%
BZD (peripheral)	<10%	$\kappa$	<10%
Bombesin	<10%	$\mu$	63%
B2	<10%	ORL 1	<10%
CGRP	<10%	PACAP-null	<10%
CB1	<10%	PCP	<10%
CB2	10%	TXA/PGH <sub>2</sub>	<10%
CCK <sub>1</sub>	<10%	PGI <sub>2</sub>	<10%
CCK <sub>2</sub>	<10%	P2X	20%
D1	<10%	P2Y	<10%
D2	<10%	5-HT <sub>1A</sub>	10%
D3	13%	5-HT <sub>1B</sub>	<10%
D4	<10%	5-HT <sub>2A</sub>	<10%
D5	10%	5-HT <sub>2C</sub>	<10%
DA transporter	<10%	5-HT <sub>3</sub>	<10%
ET <sub>A</sub>	13%	5-HT <sub>5A</sub>	<10%
ET <sub>B</sub>	<10%	5-HT <sub>6</sub>	<10%
GABA	<10%	5-HT <sub>7</sub>	<10%
Galanin	<10%	$\sigma$	<10%
PDGF	<10%	Somatostatin	<10%
IL-8A (CXCR1)	<10%	VIP	<10%
TNF- $\alpha$	<10%	V1A	<10%
CCR1	<10%	Ca <sup>2+</sup> channel (L)	<10%
H <sub>1</sub>	<10%	K <sup>+</sup> channel (voltage)	<10%
H <sub>2</sub>	<10%	K <sup>+</sup> channel (Ca <sup>2+</sup> )	<10%
ML <sub>1</sub>	<10%	Na <sup>+</sup> channel (site 2)	<10%
M1	12%	Cl <sup>-</sup> (TBPS site)	<10%

Radioligand binding studies performed at Cerep. A-429202 was assayed at 10 $\mu$ M and results are expressed as % inhibition of control specific binding. Data from Cerep study report # 860191.

Four additional receptors were analyzed in binding or FLIPR assays in house. These were the histamine H<sub>3</sub>,  $\alpha$ <sub>2c</sub> adrenergic, VR1 and P<sub>2X</sub><sub>7</sub> receptors. In binding assays A-429202 showed no effect at 1  $\mu$ M (the highest concentration used in these assays) at the human or rat histamine H<sub>3</sub> receptors and only a minimal effect at the human  $\alpha$ <sub>2c</sub> adrenergic receptor, with a K<sub>i</sub> of 1.9  $\mu$ M. In FLIPR assays, A-429202 was inactive (IC<sub>50</sub> > 100  $\mu$ M) at the human VR1 receptor and at the human or rat P<sub>2X</sub><sub>7</sub> receptors.

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## XII. *In Vivo* Pharmacology

A-429202 has been evaluated and has demonstrated efficacy comparable to ABT-594 in multiple models of nociceptive and neuropathic pain. Like ABT-594, A-429202 retains efficacy upon repeated dosing under experimental protocols where tolerance to morphine's analgesic effects develops. A-429202 is active after both i.p. and oral administration, and efficacy is correlated to drug plasma levels. Efficacy ( $ED_{50}$ ) is achieved at plasma levels of 10 to 30 ng/mL, whereas ABT-594 exhibits efficacy in the range of 3 to 6 ng/mL. Like ABT-594, A-429202 produces dose-related emesis in the ferret, but unlike ABT-594, requires a significantly greater multiple of its therapeutic plasma concentration. A-429202 requires plasma concentrations of approximately 200 ng/mL to produce emesis ( $ED_{50}$ ) in the ferret, whereas ABT-594 produces emesis ( $ED_{50}$ ) at approximately 4 ng/mL.

### A. Efficacy in Models of Nociceptive Pain

#### 1. Formalin Model of Persistent Pain

a. *Acute Administration (i.p. and oral)*: The formalin model of persistent nociceptive pain has been used extensively to characterize many classes of analgesic agents. In the standard protocol, formalin is injected into the rat's hind paw 5 minutes after administration of saline or test drug, and a biphasic response occurs consisting of an acute response (Phase I) followed approximately 30 minutes later with a persistent flinching response (Phase II). The Phase II response from time 30 to 50 minutes post formalin injection is measured. A-429202, like ABT-594 and morphine is fully efficacious in reducing flinching in this model. Analogous to the clinical experience, NSAIDs and selective COX-2 inhibitors such as Celecoxib demonstrate a "ceiling effect" in the formalin model, and generally do not reduce flinching below approximately 50% of control values (Figure 20). In that respect, the formalin model is consistent with the well-established utility of NSAIDs in the treatment of mild to moderate pain, and the lack of utility of this class in the treatment of moderately severe to severe pain.

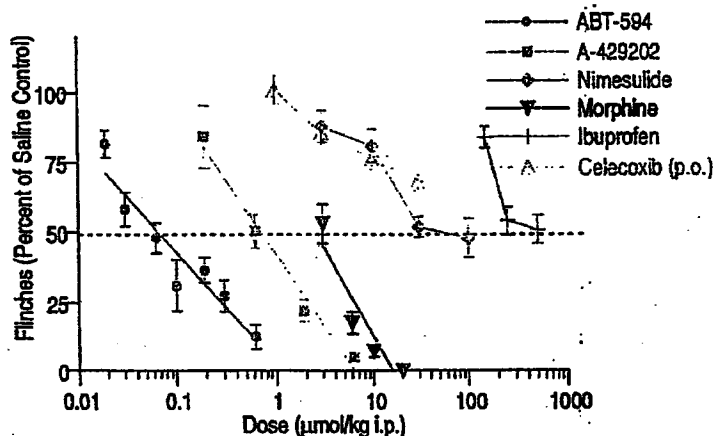


Figure 20. Comparison of A-429202 to other analgesic agents in the formalin model of persistent nociceptive pain.

A-429202 retains efficacy upon oral administration, and comparable levels of response are achieved at comparable plasma drug levels. Consistent with the pharmacokinetic data (see Section XIII), a three-fold higher dose is required to produce a comparable plasma  $C_{max}$  level, and at that dose, an equivalent 50% efficacy is achieved with either i.p. or oral administration (Figure 21).

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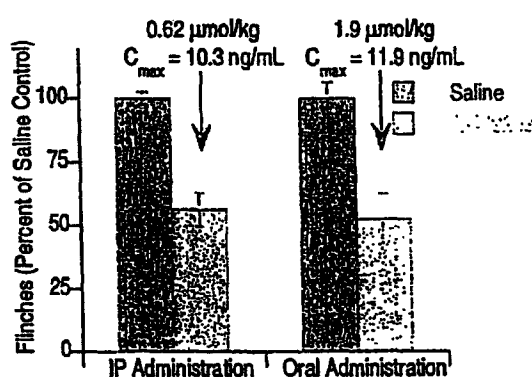


Figure 21. Retention of efficacy upon oral administration of A-429202 in the formalin persistent nociceptive pain model.

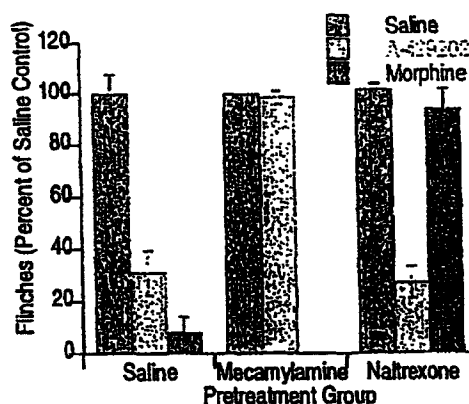


Figure 22. Antagonism of the analgesic effect of A-429202 by NNR blockade but not by blockade of  $\mu$ -opioid receptors.

b. *NNR Mechanism of Action:* The antinociceptive effects of A-429202 in the formalin pain model are antagonized by the non-selective NNR antagonist mecamylamine, but not by the  $\mu$ -opioid antagonist naltrexone (Figure 22). These data support the nicotinic mechanism of action of A-429202 and demonstrate the lack of involvement of opioid receptor pathways.

c. *Duration of Action:* To address duration of action in the formalin model, a modified protocol was used in which test compound was administered either 5 minutes, 30 minutes or 90 minutes prior to formalin injection. Efficacy was then evaluated in the period 30 to 50 minutes post-formalin injection. A-429202 (1.9  $\mu$ mol/kg, i.p.) exhibited a time-dependent decrease in efficacy (Figure 23). In a comparable experiment, ABT-594 (0.1  $\mu$ mol/kg, i.p.) was evaluated over time. The 35-minute effect was comparable for the two compounds. A-429202 exhibited a comparable degree of efficacy at 60 minutes as was observed with ABT-594 at 120 minutes, suggesting that in the rat ABT-594 exhibits a somewhat longer duration of action, consistent with the differences in pharmacokinetic properties of the two compounds.

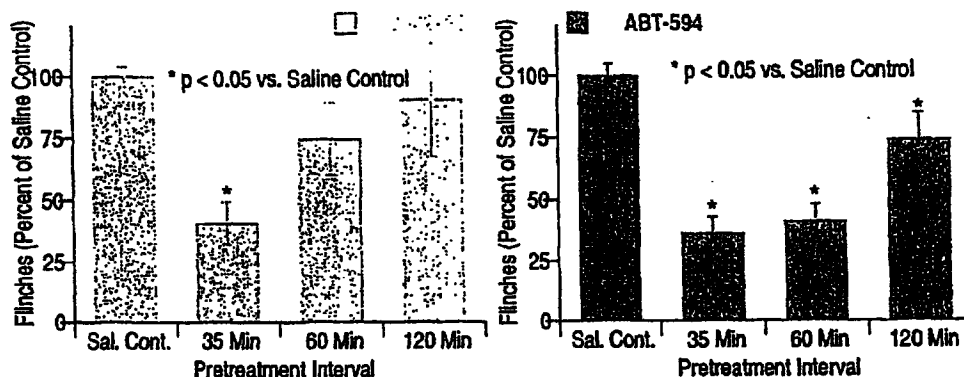


Figure 23. Duration of action of A-429202 and ABT-594 after i.p. administration in the formalin model of persistent nociceptive pain.

In a second study, a higher dose (19  $\mu$ mol/kg) of A-429202 was administered orally, and efficacy was again measured at 35, 60, and 120 minutes post-drug administration. Efficacy was maintained at all time points (Figure 24).

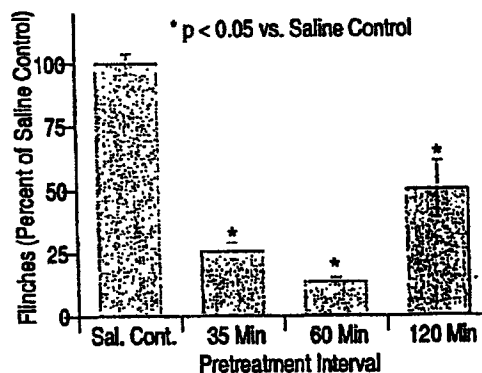
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Figure 24. Duration of action of A-429202 after oral administration in the formalin model of persistent nociceptive pain.



d. *Plasma Levels Associated with Efficacy:* From the dose-response studies in the formalin model (Figure 20),  $ED_{50}$  values for A-429202 and ABT-594 were calculated to be 0.8  $\mu\text{mol/kg}$  and 0.07  $\mu\text{mol/kg}$  respectively (11-fold potency difference). Efficacy was evaluated between 35 and 55 minutes post dosing. Plasma levels at the 30-minute time point (extrapolated from i.p. doses of 1.9  $\mu\text{mol/kg}$  and 0.1  $\mu\text{mol/kg}$  of A-429202 and ABT-594 respectively) were 9.0 ng/mL and 2.8 ng/mL for A-429202 and ABT-594 (3.2-fold potency difference). In a separate analysis, data from the duration of action study were used to estimate the plasma concentration at the time point at which efficacy crossed the 50% level (See Figure 25). The estimated plasma level for A-429202 was 18 ng/mL and the value for ABT-594 was 2.9 ng/mL, yielding a calculated potency difference of 6.2-fold. Evaluation of plasma concentrations from oral administration studies (see Figure 21) also establishes the effective plasma concentration to be within this range (plasma concentration at  $ED_{50}$  = 11.9 ng/mL). The effective plasma concentration for A-429202 in the formalin persistent pain model ranges from 9 to 18 ng/mL, whereas the effective plasma concentration for ABT-594 is consistently near 3 ng/mL.

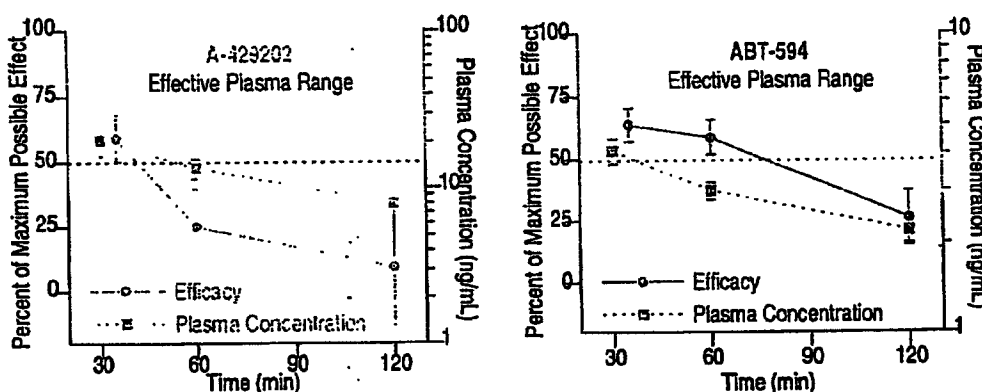


Figure 25. Association of plasma levels and efficacy over time for A-429202 and ABT-594 in the formalin model of persistent nociceptive pain.

## 2. Acetic Acid Writhing Model of Visceral Pain in Mice

In a second model of chemically induced persistent pain, A-429202 exhibits dose-dependent reversal of acetic acid induced writhing in the mouse. Like ABT-594, A-429202 is fully efficacious ( $ED_{50}$  = 0.6  $\mu\text{mol/kg}$ , i.p.) in this model and approximately 6-fold less potent than ABT-594 (Figure 26).

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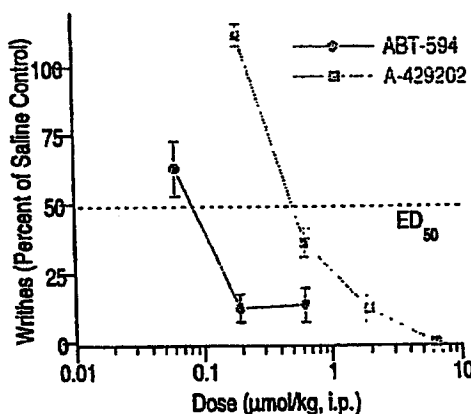


Figure 26. Analgesic effects of A-429202 and ABT-594 in the mouse abdominal constriction assay (ACA) model of visceral pain.

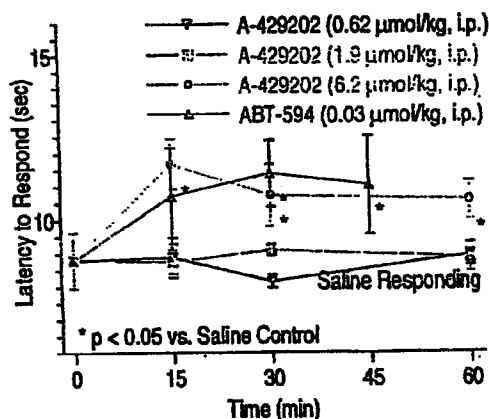


Figure 27. Antinociceptive effects of A-429202 over time in the Hargreaves Hot Box model of acute thermal pain.

### 3. Hargreaves Hot Box Model of Acute Thermal Pain

The Hargreaves hot box model assesses acute response to a painful thermal stimulus in normal, uninjured rats. A-429202 is substantially less potent than ABT-594 in this model. ABT-594 exhibits a statistically significant effect at 0.03 μmol/kg, whereas the minimally effective dose for A-429202 is 6.2 μmol/kg (Figure 27).

### 4. Carrageenan Model of Inflammatory Pain

Carrageenan-induced hyperalgesia has been widely used as a model for evaluating anti-inflammatory analgesic agents like the NSAIDs. In this model, test compound is administered, followed 30 minutes later by injection of carrageenan into the right hind paw. Two hours later, paw withdrawal latency to a noxious thermal stimulus is measured in the injured paw and compared to the uninjured paw. ABT-594 and A-429202 exhibit a modest antihyperalgesic effect in this model (Figure 28). The long delay between test compound administration and nociceptive testing (2.5 hr), in conjunction with the relatively short half-life of both of these compounds in the rat, may contribute to the relatively modest responses observed for these compounds in this model.

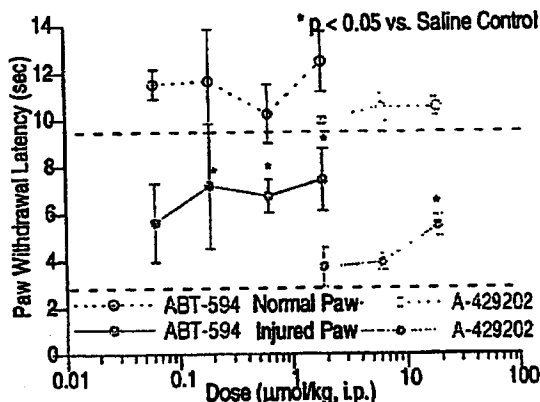


Figure 28. Effects of A-429202 and ABT-594 in the carrageenan paw inflammation model of hyperalgesia.

## B. Efficacy in Models of Neuropathic Pain

A-429202 was evaluated in two models of neuropathic pain: the Chung model of nerve-injury induced neuropathic pain and the Bennett sciatic nerve ligation model of neuropathic pain. A-429202 exhibited comparable efficacy to ABT-594 in both of these models.

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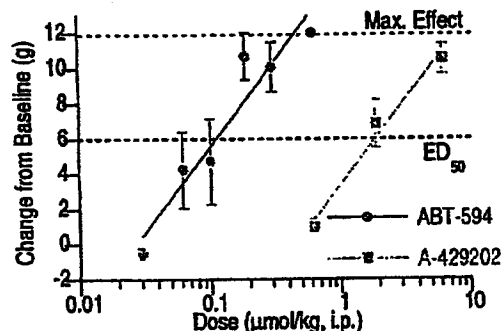
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### 1. Chung Spinal Nerve Ligation Model

In the Chung model, the spinal nerves of the L5-L6 segment are tightly ligated, and after recovery from surgery, the animals develop tactile allodynia developing within 7 days and persisting for several weeks. The tactile allodynia is assessed by measuring the threshold for injured paw withdrawal to stimulus from calibrated Von Frey hairs.

a. *Acute Administration:* A-429202 exhibits dose-dependent full efficacy in the Chung neuropathic pain model. ED<sub>50</sub> values for A-429202 and ABT-594 in the Chung model are 1.9  $\mu\text{mol/kg}$ , i.p. and 0.1  $\mu\text{mol/kg}$ , i.p. respectively (Figure 29).

Figure 29. Dose-response evaluation of maximum effects of A-429202 and ABT-594 in the Chung nerve ligation model of neuropathic pain.



b. *Repeated Administration:* A-429202 (6.2  $\mu\text{mol/kg}$ , i.p.) was compared to ABT-594 (0.3  $\mu\text{mol/kg}$ , i.p.) and morphine (21  $\mu\text{mol/kg}$ , i.p.) in a repeated dosing paradigm, in which groups of rats were dosed twice daily with either test compound or saline for 5 days. During the second dosing period of the fifth day, both vehicle and drug treated groups received active compound. Like ABT-594, the repeated dose A-429202 group retained full efficacy comparable to the saline treated control group (Figure 30). The repeated-dosing morphine group, however, exhibited markedly lower efficacy vs. the saline-treated control group. This experiment suggests that A-429202 has less potential to develop tolerance compared to morphine.

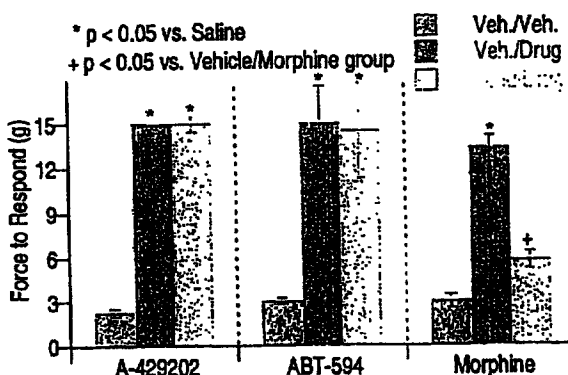


Figure 30. Comparison of A-429202 to ABT-594 and morphine after acute and repeated dosing in the Chung nerve ligation model of neuropathic pain.

c. *Duration of Action:* Upon i.p. administration in the Chung model, A-429202 exhibits a short duration of action, with significant efficacy observed only at the 15 minute time point. Although ABT-594 also exhibits a relatively short duration of action, efficacy is retained through 30 minutes in the low dose study and through 60 minutes in the high dose study (Figure 31).

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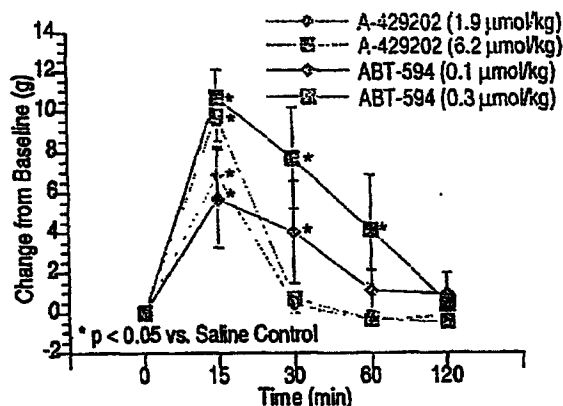


Figure 31. Comparison of the duration of action of equi-effective doses of A-429202 and ABT-594 in the Chung nerve ligation model of neuropathic pain.

To address whether the short duration of effect of A-429202 in the Chung model represents tachyphylaxis, as it is well documented that a single nicotine exposure induces short-lived tolerance to its psychoactive and cardiovascular effects,<sup>19</sup> the following experiment was designed. A-429202 (6.2 µmol/kg, i.p.) or saline was administered at time zero. At time 40 min, when the initial antiallodynic effects were no longer evident, a second dose (6.2 µmol/kg, i.p.) was administered. The groups receiving A-429202 followed by saline, or saline followed by A-429202, exhibited a short-duration antiallodynic response consistent with the original experiments. The group receiving the two consecutive drug doses, however, exhibited a long-lasting antiallodynia that was still maximal one hour past the administration of the second dose (Figure 32). These results argue against a rapid tachyphylaxis to the antiallodynic effects. Pharmacokinetic experiments are ongoing to better understand this phenomenon.

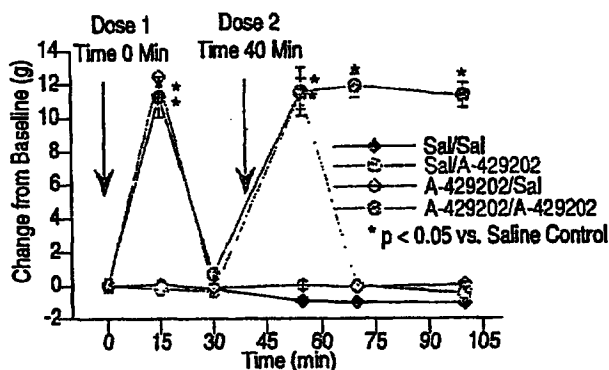


Figure 32. Evaluation of A-429202 in a double-dosing paradigm to evaluate potential tachyphylaxis to the antiallodynic response.

## 2. Bennett Sciatic Nerve Injury Model

A-429202 was evaluated in a second model of neuropathic pain. In the Bennett model, loose ligature of the sciatic nerve results in the development of tactile allodynia. The Bennett model differs from the Chung model, in that inflammation is believed to be a more important component of the Bennett model.<sup>20,21</sup> A-429202 and ABT-594 exhibit a dose-dependent reversal of allodynia in this model. Both compounds exhibit the same difference in potency in the Bennett model as had previously been observed in the Chung model. However, both compounds are less potent in this model vs. the Chung model (Figure 33).

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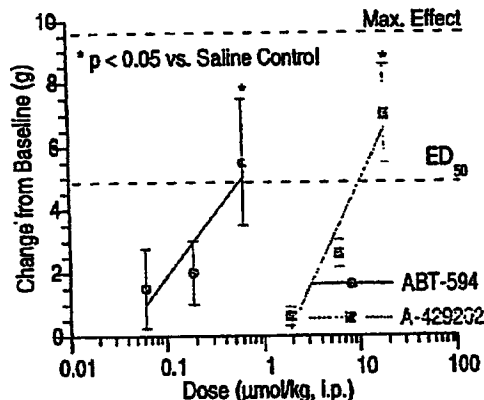
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# Meyer Deposition Exhibit 27

P's Exhibit GN – Part 2

Figure 33. Evaluation of A-429202 and ABT-594 in the Bennett sciatic nerve injury model of neuropathic pain.



### C. Anticipated Emesis Liability Within Therapeutic Dose Range

Nausea and emesis are the key adverse events associated with ABT-594 that have limited the therapeutic potential of this drug. The key attribute that distinguishes A-429202 from ABT-594 relates to a reduced emetic liability and the resultant improvement in predicted therapeutic index. The preclinical data supporting that conclusion will be discussed in this and the following sections. The remainder of the safety pharmacology will be addressed in Section XIV of this document.

The ferret has been extensively evaluated as a preclinical model of emesis, primarily for the identification and characterization of anti-emetic agents. Dose-response studies with ABT-594 in the ferret have been predictive of the emetic liability observed clinically, with an excellent correlation between plasma levels in humans and ferret required to produce emesis (Figure 34). The correlation is best between the hard gelatin capsule (HGC) Phase I studies and the ferret studies. The earlier clinical experience with solution dosing demonstrated poorer tolerability and predicted emesis at lower plasma concentrations.

Dose-response studies have been conducted to evaluate the relative potency and efficacy of A-429202 and ABT-594 to produce emesis in the ferret. These two compounds did not produce parallel dose response curves, with the dose-based potency difference of 30-fold at the no-emesis dose and 160-fold at the maximal emesis dose. The potency difference at 50% emesis was approximately 100-fold (Figure 35, Panel A). The severity of the emesis differed between the two compounds, and these data are captured in the emesis index calculations (Emesis Index = Total # of emetic episodes x fraction of animals exhibiting emesis). For example, at a dose of 10 μmol/kg A-429202, 5 of 6 ferrets (83%) exhibited emesis, with 6 total emetic episodes among the 5 animals, resulting in an EI = 5. Whereas, at a dose of 0.1 μmol/kg ABT-594, 5 of 6 ferrets (83%) exhibited emesis, with 23 total emetic episodes for EI = 19.2 (Figure 35, Panel B).

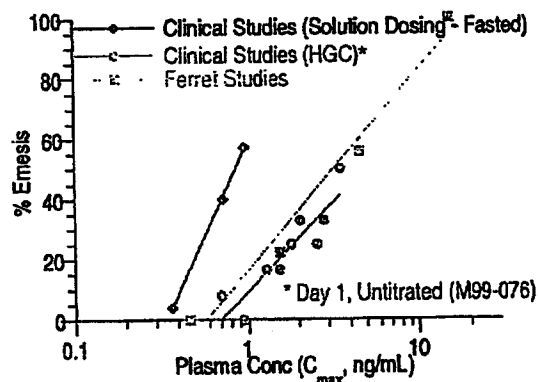


Figure 34. Correlation of plasma levels associated with emesis in preclinical ferret studies with results from Phase I clinical studies with ABT-594.

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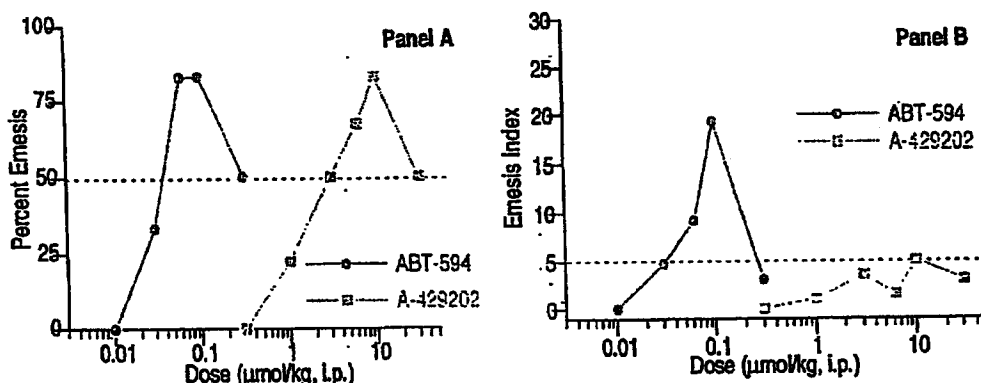


Figure 35. Evaluation of emesis liability using analyses based on percent of animals exhibiting emesis and severity of emesis using emesis index in the ferret for A-429202 and ABT-594—acute administration studies.

Based on the approximately 100-fold potency difference derived from the acute dosing studies, ABT-594 and A-429202 were compared in a repeat dosing protocol. Two groups of ferrets ( $n=6$  per group) received either 0.062  $\mu\text{mol/kg}$ , i.p. ABT-594 or 6.2  $\mu\text{mol/kg}$ , i.p. A-429202 twice daily for five days. Animals were allowed free access to food and water throughout the study (fasted ferrets were used for the acute studies). Dose selection was based on a best estimate of an equi-emetic dose, and not an equi-effective analgesic dose. A dose of 0.062  $\mu\text{mol/kg}$  ABT-594 is marginally effective in the Chung and formalin models, whereas a dose of 6.2  $\mu\text{mol/kg}$  A-429202 is nearly maximally effective in these two models (See Figure 29 and Figure 20). Emesis was consistently more apparent during the first dosing period of each day, and data from that morning period are summarized in the graphs below. Throughout the duration of the study, ferrets receiving ABT-594 continued to exhibit emesis behavior, and although the frequency and severity did decrease from the first day, emesis continued through day 5. The animals receiving A-429202 exhibited less emesis on day 1 (50% vs. 83%), and by day 3, emesis was no longer observed (Figure 36, Panel A). Analysis based on emesis index and nausea behavior scoring (Figure 36, Panel B) accentuated the difference between the two compounds. Based on this experiment, the potency difference to produce emesis and related behaviors is greater than 100 fold. While these studies suggest that A-429202 has less emetic liability than ABT-594 following repeated dosing, clinical studies using an optimized formulation will be necessary to define the optimal dose titration protocol (if required).

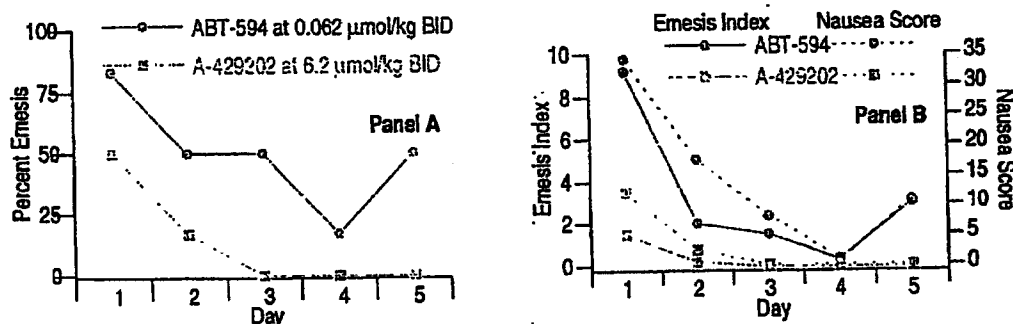


Figure 36. Comparison of emesis liability of A-429202 and ABT-594 upon repeated administration in the ferret (Dosing from AM dosing period shown).

#### D. Therapeutic Index vs. Emesis Liability

Because analgesic efficacy values are derived from rat studies and emesis liability is evaluated in the ferret, it is necessary to normalize therapeutic index calculations to plasma levels rather than dose. In the ferret, A-429202 is characterized by initial high plasma levels after i.p. administration and a short half-life (1 hr). In the rat, an equivalent dose of A-429202 produces significantly lower peak plasma levels relative to the ferret (Figure 37). A-429202 exhibits low plasma protein binding (24 and

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38%) in both rat and ferret, and cannot account for this difference. In addition, overall drug exposures (as measured by AUC) are within a factor of 2 between the ferret and rat. However, at the critical early time points when efficacy is being measured and emesis is occurring, equivalent doses of A-429202 produce >10-fold higher plasma levels in the ferret vs. the rat (from an i.p. dose of 1.9  $\mu\text{mol/kg}$ : at  $t = 15$  min, ferret levels are 282 ng/mL and rat levels are 18.1 ng/mL). ABT-594, at equivalent dose, produces only marginally higher levels in the ferret. Overall exposure (AUC) is nearly identical, but initial plasma exposure is higher (from an i.p. dose of 0.1  $\mu\text{mol/kg}$ : at  $t = 15$  min, ferret levels are 10.8 ng/mL and rat levels are 4.5 ng/mL). These observations highlight the need to appropriately adjust for pharmacokinetic differences across species when assessing therapeutic index based on behavioral measures from different species.

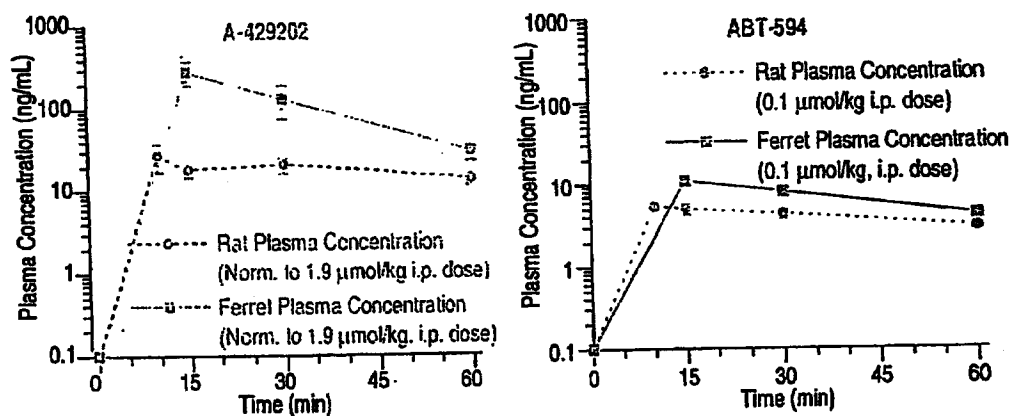


Figure 37. Dose-adjusted plasma levels for A-429202 and ABT-594 in rat and ferret.

### 1. Therapeutic Index: Nociceptive Pain (Formalin Model) vs. Emesis

Calculated on plasma exposure, the improvement in therapeutic index for A-429202 vs. ABT-594 based on efficacy in the formalin model vs. emesis liability is approximately 30-fold (Figure 38). The ratio of plasma levels at  $\text{ED}_{50}$  for emesis and efficacy for A-429202 and ABT-594 respectively are 36 and 1.1. At a plasma level anticipated to produce no emesis, efficacy in the formalin model would be expected to be approximately 80% of the maximally achievable response for A-429202, but less than 20% for ABT-594. Based on dose,  $\text{ED}_{50}$  values for A-429202 and ABT-594 in the formalin model are approximately 0.8  $\mu\text{mol/kg}$  and 0.07  $\mu\text{mol/kg}$  respectively (Figure 20). Dose-based  $\text{ED}_{50}$  values for emesis response in the ferret are 3  $\mu\text{mol/kg}$  and 0.05  $\mu\text{mol/kg}$  for A-429202 and ABT-594 respectively (Figure 35). These values result in an approximately 5-fold dose-based improvement in therapeutic index for A-429202 vs. ABT-594.

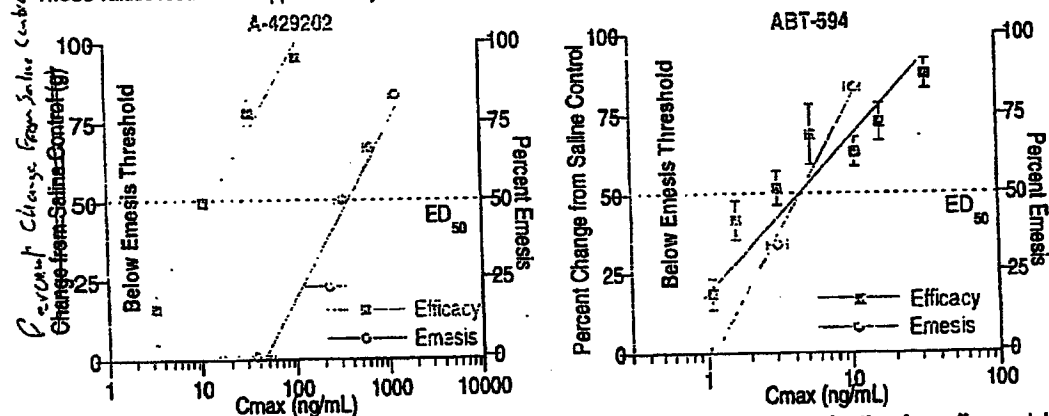


Figure 38. Plasma concentration-response curves for A-429202 and ABT-594 in the formalin model of persistent nociceptive pain and the ferret emesis model.

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## 2. Therapeutic Index: Neuropathic Pain (Chung Model) vs. Emesis

Using a similar comparative analysis, the plasma level based analysis yields an improvement in therapeutic index of approximately 13-fold (Figure 39). Relating these data to the clinical results from ABT-594, the top dosing group (300  $\mu$ g, BID) achieved  $C_{max}$  plasma levels of approximately 3 ng/mL, which in the Chung model correlates to a response of slightly less than 50% of a maximally achievable response. At that plasma level, greater than 50% of subjects were discontinuing treatment due to nausea and vomiting. The preclinical results suggest that this plasma level (3 ng/mL) will produce emesis in 30 to 40% of ferrets. Applying this same analysis to the results from A-429202 in these two models, a plasma level that produces >50% efficacy (30 – 40 ng/mL) in the Chung model will be non-emetic. Using a dose-based analysis of  $ED_{50}$  values from the Chung model and from the emesis model yields an improvement in therapeutic index for A-429202 of about 3.5-fold over ABT-594.

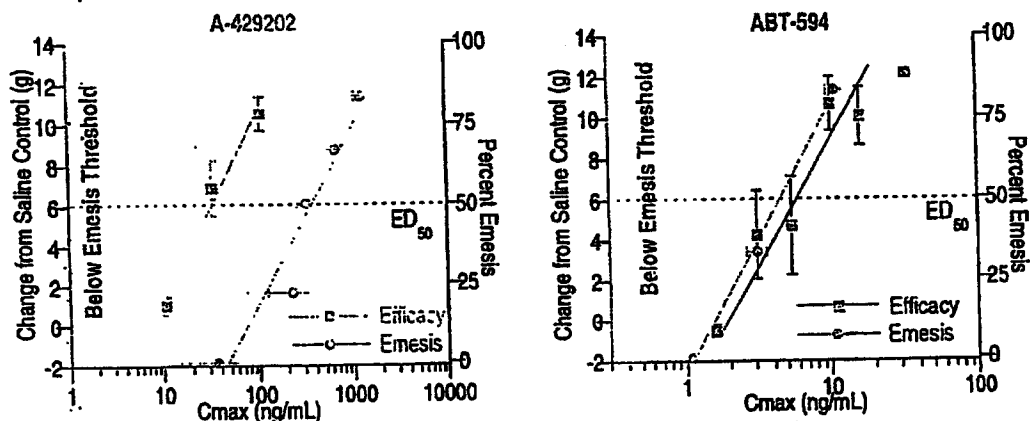


Figure 39. Plasma concentration-response curves for A-429202 and ABT-594 in the Chung model of neuropathic pain and the ferret emesis model.

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### XIII. Pharmacokinetics and Metabolism

A-429202 is rapidly cleared from rat, dog and monkey after i.v. administration, with half life ranging from 0.7 to 2.0 hours and CL<sub>p</sub> ranging from 1.7 to 5.1 L/hr·kg. Oral bioavailability ranges from 22% in monkey to 52% in rat. In the rat, AUC values are relatively linear across dose, and do not accumulate significantly after repeated dosing. In rat, A-429202 partitions into the brain, with peak concentrations 5-6 fold higher than in the plasma. In the rat, A-429202 is largely renally eliminated (approx. 50% of total dose), and approximately 50% of that is as parent drug. *In vitro* metabolism studies indicate a predominant role for phase I metabolism. However, additional clearance mechanisms (e.g. renal and/or secretion) are likely providing a significant contribution to overall clearance. Cytochrome P450 interaction studies show that the CYP2D6 isoform is primarily responsible for the metabolism of A-429202. Although A-429202 is an inhibitor of CYP2D6, the effect is weak at anticipated therapeutic plasma concentrations of 10 to 30 ng/mL and significant drug-drug interactions due to CYP2D6 inhibition by the agent are not anticipated. Human pharmacokinetic behavior has been projected with physiologically-based models and Trial Simulator. An average human clearance of 45 L/hr and a terminal phase half-life of 6 to 10 hours are predicted, a profile consistent with twice daily dosing.

#### A. Pharmacokinetic Studies

The pharmacokinetics of A-429202 were evaluated in Sprague-Dawley rat, ferret, beagle dog and cynomolgus monkey. A-429202 concentrations declined rapidly after intravenous dosing in all three species tested, with plasma clearance values ranging from 1.7 L/hr·kg in the monkey to 5.1 L/hr·kg in the rat (see Figure 40). The high plasma clearance values are partially explained by the high volumes of distribution, with V<sub>D</sub> values ranging from 2.0 L/kg in the monkey to 15.4 L/kg in rat. Plasma elimination half-lives were less than 2 hours in all species. Quantitative availability was noted following a 1.9 µmol/kg IP dose in rat. Oral bioavailability values were lower, ranging from 22.1% in the monkey to 52.4% in rat. Bioavailability values remained constant at higher (5, 15 or 30 mg/kg) oral doses in rat, with values between 61-65%. Species dependent and dose dependent differences were noted in the rate of absorption after oral administration. A-429202 was rapidly absorbed from lower oral doses in rat, with *t*<sub>max</sub> values of <1 hour (see Figure 40(A)); *t*<sub>max</sub> values tended to increase with increasing dose in the rat. The absorption of A-429202 from a solution dose was slow in the dog, with an average *t*<sub>max</sub> value of 3.7 hours (see Figure 40(B)).

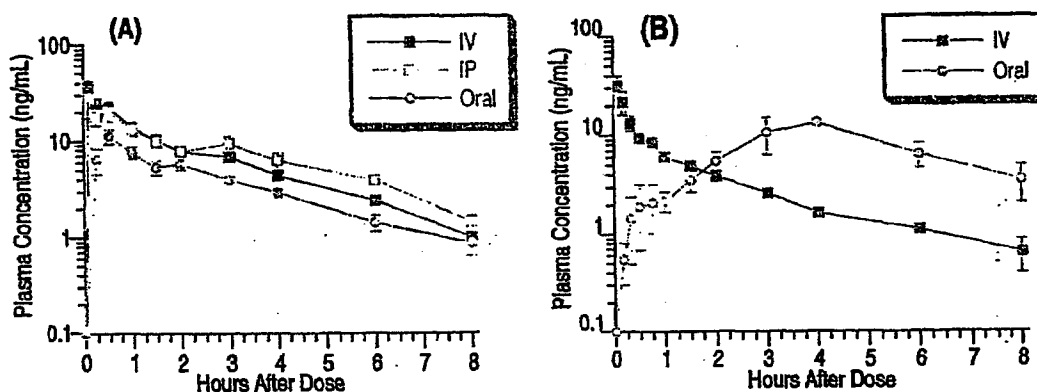


Figure 40. (A) Mean ( $\pm$ SEM, n=3) A-429202 plasma concentrations after a 1.9 µmol/kg intravenous, intraperitoneal or oral dose in rat. (B) Mean ( $\pm$ SEM, n=3) A-429202 plasma concentrations after a 0.5 µmol/kg intravenous or 3 µmol/kg oral dose in dog.

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Table 14. Pharmacokinetics of A-429202 after a Single Dose in Rat, Ferret, Monkey and Dog

Intravenous Dose										
Species	Dose		$t_{1/2}$	$V_c$	$V\beta$	$AUC_{0-\infty}$	$CL_p$	n		
	( $\mu\text{mol/kg}$ )	( $\text{mg/kg}$ )	(hr)	(L/kg)	(L/kg)	( $\text{ng}\cdot\text{hr/mL}$ )	(L/hr/kg)			
Rat	1.9	0.310	2.0	7.8	15.4	60.9	5.1	3		
Monkey	0.25	0.041	0.7	1.1	2.0	26.1	1.7	3		
Dog	0.5	0.082	1.9	2.8	7.8	30.6	2.7	3		
IP or Oral Dose										
Species	Dose			$t_{1/2}$	$C_{max}$	$t_{max}$	$AUC_{0-\infty}$	F	n	
	( $\mu\text{mol/kg}$ )	( $\text{mg/kg}$ )	Route	(hr)	( $\text{ng/mL}$ )	(hr)	( $\text{ng}\cdot\text{hr/mL}$ )	(%)		
Rat	1.9	0.310	IP	2.0	32.6	0.3	65.9	108	3	
	1.9	0.310	PO	2.1	11.9	0.7	31.9	52.4	3	
	30.6	5	PO	6.7	73.8	1.0	640	65.2	3	
	91.9	15	PO	8.6	174.2	2.2	1917	65.1	3	
	183.8	30	PO	11.2	250.4	2.5	3613	61.4	3	
Ferret	0.3	0.049	IP	0.8	35.8	0.5	21.2	uc	3	
	1.0	0.163	IP	1.0	224.8	0.25	132.1	uc	3	
	3.0	0.490	IP	1.3	320.2	0.25	186.1	uc	3	
Monkey	1.0	0.163	PO	1.2	12.1	1.3	23.1	22.1	3	
Dog	3.0	0.490	PO	1.9	15.5	3.7	71.6	39.0	3	
Selected Comparative Values of ABT-594 and ABT-089										
ABT-594		IV Parameters				Oral Parameters				
Species	$t_{1/2}$	$V_c$	$V\beta$	$CL_p$	Dose	$t_{1/2}$	$t_{max}$	$C_{max}$	$AUC_{0-\infty}$	%F
	(h)	(L/kg)	(L/kg)	(L/hr/kg)	( $\mu\text{mol/kg}$ )	(h)	(h)	( $\text{ng/mL}$ )	( $\text{ng}\cdot\text{hr/mL}$ )	
Rat	1.5	3.5	3.6	1.7	0.30	2.1	1.5	4.8	21.2	60.6
Monkey	1.4	2.7	3.5	1.7	0.10	UC	2.2	2.4	9.9	80.4
Dog	4.7	1.5	3.1	0.4	0.10	4.2	0.8	3.2	18.0	35.2
Human <sup>a</sup>	-	-	2.0 <sup>b</sup>	0.18 <sup>b</sup>	100 $\mu\text{g}$	8.2	2.5	0.66	8.39	-
ABT-089		IV Parameters				Oral Parameters				
Rat	1.1	3.0	5.5	3.4	2.0	3.6	0.6	9.3	38.0	33.4
Monkey	2.1	3.5	7.5	2.5	0.20	1.7	2.7	1.0	4.6	23.4
Dog	1.8	2.9	5.0	2.0	0.50	1.7	0.8	9.4	28.0	61.5
Human	-	-	-	-	10 mg <sup>c</sup>	8.6	1.9	26.7	280	-

Route: route of administration [po = oral; IP – intraperitoneal]. UC = unable to calculate.

<sup>a</sup> Averaged composite results from three trials using 100  $\mu\text{g}$  oral solution dose and two trials using 80  $\mu\text{g}$  oral solution dose.<sup>b</sup> Values derived assuming 75 kg average weight, data derived from oral administration.<sup>c</sup> Results from 11 dosing groups from 2 to 60 mg (n=85 subjects) normalized to an oral dose of 10 mg ( $C_{max}$  and AUC were highly dose-proportional across dosing groups).

A-429202 was also variably absorbed from higher (10, 30 or 60  $\text{mg/kg/day}$  for 14 days) oral doses in rat, with peak concentrations noted from one to twelve hours after drug administration (see Table 15). Peak plasma concentrations increased in a manner less than proportional to the increase in dose on the first day of dosing. Peak concentrations after fourteen days of dosing were similar to those noted after the first dose in the 10 and 30  $\text{mg/kg/day}$  treatment groups, but were more than two-fold higher in the 60  $\text{mg/kg/day}$  dose group at the end of the study. AUC values tended to increase in a more linear manner with increasing doses after both single and multiple doses. AUC values in the 10 and 30  $\text{mg/kg/day}$  dose groups after multiple daily dosing were similar to or slightly lower than those recorded after a single oral dose. However, AUC values in the 60  $\text{mg/kg/day}$  dose group were approximately 30% higher after multiple dosing when compared to single dose data. No significant or consistent trends were noted in the data obtained from male vs. female rats in this multiple dose study.

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Table 15. Pharmacokinetics of A-429202 after a Multiple Oral Dosing in Rat

Dose ( $\mu\text{mol/kg}$ ) (mg/kg)*	Day	Route	$t_{1/2}$ (hr)	$C_{\text{max}}$ (ng/mL)	$C_{\text{max}}/D$	$t_{\text{max}}$ (hr)	$\text{AUC}_{0-\infty}$ (ng·hr/mL)	$\text{AUC}/D$	n
61.3	0	PO	3.6	210	21.0	3.0	2099	210	6
10	13	PO	4.0	190	19.0	2.0	2211	221	6
183.8	0	PO	7.4	352	11.7	2.7	5688	190	6
30	13	PO	6.4	326	10.9	1.3	4566	152	6
367.6	0	PO	11.5	368	6.1	3.3	8395	140	6
60	13	PO	8.7	921	15.4	6.8	11695	195	5

\* mg parent/kg/day administered as the tosylate salt.

 $C_{\text{max}}/D$  – ng/mL per mg/kg/day;  $\text{AUC}/D$  (ng·hr/mL per mg/kg/day).

A-429202 rapidly distributed into the brain after i.p. dosing in rat, with peak concentrations 5-6 fold higher than the plasma concentrations (Figure 41). The apparent elimination half-life in the brain (6-7 hours) was longer than the plasma elimination half-life (1.5-2 hr). A-429202 brain AUC values were ~20-fold higher than the corresponding plasma values. However, concentrations of A-429202 in the brain did not appear to accumulate following six once-daily 6.2 (see Figure 41) or 0.62 (data not shown)  $\mu\text{mol/kg}$  i.p. doses in rat.

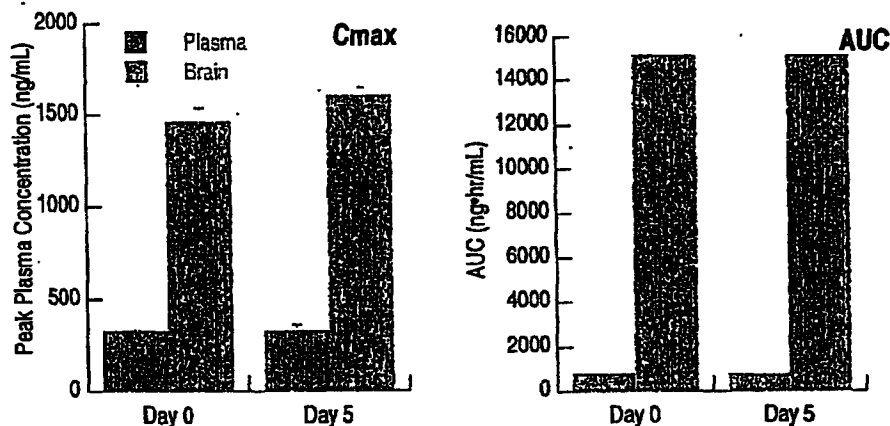


Figure 41. Mean ( $\pm$ SEM, n=3) A-429202 peak plasma and brain concentrations ( $C_{\text{max}}$ ) and area under the curve (AUC) values after a single (Day 0) or six (Day 5) 6.2  $\mu\text{mol/kg/day}$  i.p. doses in rat.

## B. Metabolism Studies

### 1. In vivo studies:

The *in vivo* metabolism of [ $^3\text{H}$ ] A-429202 was investigated in Sprague-Dawley male rats after a single intravenous (30.6  $\mu\text{mol/kg}$ ) or oral (61.3  $\mu\text{mol/kg}$ ) administration. Elimination of total dose radioactivity was rapid with an average of 65% excreted in the urine (including cage wash) and feces within 24 h.

Of this total dose radioactivity, approximately 54% was excreted in the urine and 11% in the feces, within 24 h for both intravenous and oral administration. These results suggest that renal excretion is probably the major mechanism for elimination of A-429202 and its metabolites in rat.

Radiochemical analysis of urine and feces from treated rats indicated the presence of parent drug and up to 6 metabolites (M1 to M6) and tritiated water. Of these metabolites M4 and tritiated water were clearly the most predominant in urine, accounting for an average of 7.0% and 6.7% after intravenous and 5.9% and 6.9% after oral

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administration, of the total dose radioactivity, respectively. Parent drug accounted for 21% of the total dose radioactivity after either administration. In the feces the metabolite M1 accounted for 2.6% (iv) and 5.0% (p.o) of the total dose radioactivity.

The metabolism of [ $^3\text{H}$ ] A-429202 was also investigated in bile-cannulated male rats following a single intravenous (30.6  $\mu\text{mol/kg}$ ) or oral (61.3  $\mu\text{mol/kg}$ ) administration. The bile, which accounted for 3.2% (iv) and 4.8% (po) of total dose radioactivity, primarily consisted of the metabolite, M3 and tritiated water.

Following oral administration, total radioactivity was slowly absorbed with a time to maximum plasma concentration ( $t_{\text{max}}$ ) of 6 h. The estimated fraction of parent absorbed was 84%. Elimination of parent drug was very rapid with the elimination half-time ( $t_{1/2}$ ) of 1.6 h and 1.5 h for the iv and po administration, respectively (consistent with the pre-clinical PK data). The major metabolite detected by HPLC analysis with radio-chemical detection was tritiated water. Furthermore, tritiated water was detectable in brain, heart, lung, liver, spleen, intestine and fat.

## 2. In vitro studies:

When [ $^3\text{H}$ ]A-429202 was incubated with rat, dog, monkey or human microsomes at 1  $\mu\text{M}$  (163 ng/mL), the rate of metabolism was 5.7, 7.5 and 1.9 pmol/mg/min for human, dog and rat liver microsomes, respectively. Metabolism by human, dog and rat hepatocytes largely confirmed these findings. In these incubations tritiated water was the only metabolite observed. In contrast, incubations with monkey microsomes and hepatocytes, generated additional metabolites (M8 to M12, all unidentified at this point).

Kinetic analysis using rat, dog and human liver microsomes resulted in intrinsic clearance ( $V_{\text{max}}/K_m$ , when  $[S] \ll K_m$ ) values of 0.31 (n=2), 0.96 (n=2) and 0.48 L/hr/kg (n=3), respectively. In comparison, measured intrinsic clearance from rat (0.37 L/hr/kg) and human (0.33 L/hr/kg) hepatocytes showed a good correlation with the results obtained in microsomes, indicating a predominant role for phase I metabolism.

## 3. Cytochrome P450 Interactions

[ $^3\text{H}$ ]A-429202 (1  $\mu\text{M}$ ) was incubated with six cDNA-expressed human cytochrome P450 isoform supersomes to identify the isoforms responsible for the *in vivo* metabolism (Figure 42). The results of this experiment indicate that CYP2D6 may play an important role in the oxidative metabolism of A-429202.

To further evaluate the predominance of CYP2D6 on the metabolism of A-429202 in human liver microsomes,  $V_{\text{max}}$  and  $K_m$  were measured with and without quinidine (0.5  $\mu\text{M}$ ), a specific and potent inhibitor of CYP2D6. These results (Table 16) showed a significant reduction in CL<sub>int</sub> ( $V_{\text{max}}/K_m$ ) of 87% (from 0.0091 to 0.0012 mL/min/mg) and confirm CYP2D6 as a major enzyme in the metabolism of A-429202.

To determine the potential of drug-drug interactions in patients receiving A-429202, the inhibition of cytochrome P450-dependent monooxygenase activities by A-429202 in human liver microsomes was examined using isoform-specific substrates. A-429202 inhibited CYP2D6 (dextromethorphan O-demethylation) activity by 19.2% and 66.8% at the concentrations 3.2  $\mu\text{M}$  and 32  $\mu\text{M}$ , respectively. No significant inhibition of CYP1A2, 2A6, 2C9, 2C19, 3A4 or 2E1 was observed (Table 17). These data suggest that a clinically significant drug-drug interaction due to inhibition of CYP-mediated biotransformation of co-administered drugs is unlikely in humans at the proposed therapeutic plasma concentrations (10 to 30 ng/mL).

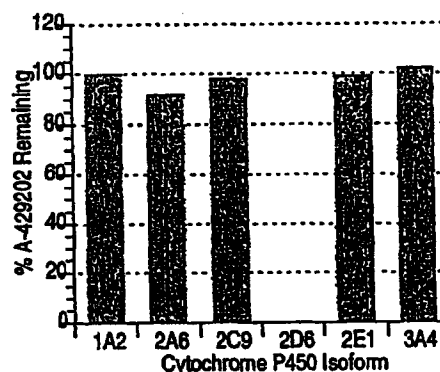


Figure 42. Percentage of parent remaining after incubation with cDNA-expressed human cytochrome P450 isoforms.

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Table 16. Apparent Michaelis-Menten parameters and hepatic intrinsic clearance of A-429202 with and without addition quinidine (0.5  $\mu$ M) in rat human liver microsomes

	K <sub>m</sub> ( $\mu$ M)	V <sub>max</sub> (pmol/min/mg)	CL <sub>int</sub> (mL/mg/min)
- quinidine	2.8	25.6	0.0091
+quinidine	1700.2	1973.7	0.0012

Table 17. Percentage of CYP inhibition by A-429202 in Human Liver Microsomes

CYP	Assay	% Inhibition by A-429202	
		3.2 $\mu$ M	32 $\mu$ M
1A2	Phenacetin O-deethylation	6.4	12
2A6	Coumarin 7-hydroxylation	0.0	10.4
2C9	Tolbutamide hydroxylation	0.0	4.4
2C19	S-Mephenytoin 4'-hydroxylation	2.8	0.0
2D6	Dextromethorphan O-demethylation	19.2	66.8
3A4	Terfenadine hydroxylation/carboxylation	0.0	0.0
2E1	Chlorzoxazone 6-hydroxylation	1.8	6.5

#### 4. Projection of Human Pharmacokinetics

Several approaches were taken to project the pharmacokinetics of A-429202 in humans, including allometric scaling, and scaling based on *in vitro* turnover in human microsomes and hepatocytes. The oral clearance (CL/F) of A-429202 is a function of the projected clearance after IV administration (CL) and the fraction of the dose systemically available (F). The latter term is the product of the fraction of the dose absorbed, and the fractions surviving first pass intestinal and hepatic metabolism:  $F = f_{abs} \cdot f_g \cdot f_{hep}$ .

**Fraction of dose absorbed ( $f_{abs}$ ):** A-429202 has two basic functional groups with pK<sub>a</sub> values of 6.1 and 8.8, and is highly soluble at physiologic pH. At the pH of the small intestine (6-7.4), logD ranges from -2.5 to -0.75, carrying with this the expectation that permeation might be restricted due to the small fraction unionized. By precedents, compounds with negative logDs tend to be incompletely absorbed. However CACO-2 experiments indicate  $P_{app}$  values in excess of  $10^{-6}$  cm/sec, which are usually associated with good absorption. The CACO experiments indicated increased permeation with lower concentrations and higher apical pH values. *In vivo*, absorption was estimated to be 84% in rat. F values ranged from >60% in rat to as low as 22% in monkey.  $T_{max}$  after solution dosing was quite variable across species, ranging from less than 1 h in rat to almost 4 h in dog.

Simulations with sensitivity analyses were conducted with GastroPlus software, which takes into account human gastrointestinal physiology and drug physicochemical characteristics. From these come the expectation that  $f_{abs}$  of A-429202 will be in the 60 to 85% range, and that this will be principally dependent on intestinal pH and transit times, colonic absorption, and the inherent effective permeability.  $T_{max}$  for solution dosing is expected to be 2 hours or less. The absorptive behavior is expected to be similar to that of ABT-594, which has similar physicochemical characteristics.

**Clearance:** Allometric plots of CL vs. weight were evaluated for A-429202 as well as analogues ABT-418, ABT-594, ABT-259 and ABT-089. The PK characteristics of A-429202 were most like those of ABT-089, which has a CL/F of approximately 45 L/h. In general, the human CL/F values of these agents are lower than predicted by the allometric regressions. From these collective data, a CL/F value in the range of 40-60 L/h would be expected.

The human CL/F for A-429202 was also predicted by scaling from *in vitro* metabolic data from human hepatocytes and microsomes, also taking into account contributions from renal elimination. As noted in a preceding section, the scaled hepatic intrinsic clearance of A-429202 based on microsomal turnover was approximately 0.48 L/h/kg, or 34 L/h for a 70 kg person. The highest turnover, equivalent to CL<sub>int</sub> of 49 L/h was obtained in microsomes rich in CYP2D6. From the CL<sub>int</sub>=34 L/h value, the extent of hepatic first pass metabolism based on the well-stirred model is projected to range from 20% in the case of restrictive protein binding to 40% (nonrestrictive binding) of the administered dose.

With the negative logD at pH 7.4, and low protein binding, it would be expected that renal elimination will supplement hepatic turnover by 7 to 15 L/h, depending on the relative contributions of glomerular filtration and tubular secretion.

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Using a renal clearance ( $CL_R$ ) of 12 L/h, and a hepatic clearance of 14 L/h, the anticipated IV clearance is approximately 26 L/h. The oral clearance ( $CL/F$ ), taking into account 70% absorption efficiency and 80% survival from hepatic first pass ( $F=0.56$ ), would be projected to be approximately 46 L/h. For individuals with high GFRs and expressing high levels of CYP2D6, it is conceivable that  $CL/F$  could exceed 100 L/h. Conversely, the highest exposure is projected for subjects with low GFR and CYP2D6 expression.

The apparent terminal distribution volume,  $V_\beta$ , for A-429202 ranged widely across species, from 2 (monkey) to 15.4 L/kg (rat). This presents considerable uncertainty in the projection of the human distribution volume, and hence the terminal half-life. With a human distribution volume of 2-3 L/kg, the terminal-phase half-life is expected to be in the 6 to 10 hour range for the average patient, thus probably meeting the commercial profile criterion for twice-daily dosing.

CYP2D6 is highly variably expressed across the population, with over 70 variant alleles described in the literature. Individuals homozygous in some of the variants (eg, CYP2D6\*4) express no functional enzyme. Phenotypically, around 5-7% of Caucasians are classified as poor metabolizers (PMs) as a result of these variants. With some drugs that are nearly exclusively eliminated by CYP2D6, the AUC ratios between PMs and extensive metabolizers (EMs) exceed 8:1. The PM/EM ratio for A-429202, an important metric to be assessed in the Phase I studies, will depend on the relative contributions of CYP2D6 versus other clearance pathways, including renal elimination. To better assess the potential population variability with A-429202 and the therapeutic and adverse consequences, clinical trial simulations have been conducted, taking into account CYP2D6 allele frequencies, as well as projected population variability in renal function and pharmacodynamic responses (derived from ABT-594 Phase II trials).

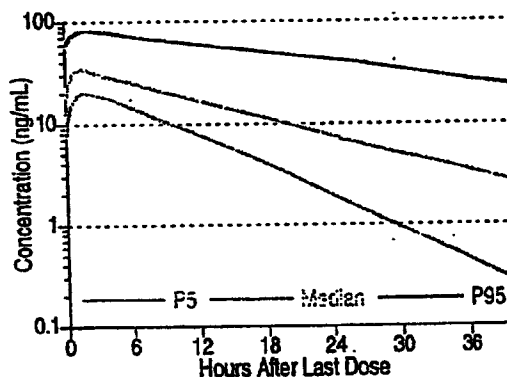


Figure 43. Simulation of Steady-State Plasma Concentration of A-429202 after 1 Week of 15 mg BID Dosing Regimen.

The results for one set of simulations with  $n=100$  subjects, with central values for  $V_\beta=3$  L/kg,  $f_{abs}=0.7$ ,  $CL_R=12$  L/h, and  $CL_{2D6}=17$  L/h, are provided (Figure 43) for steady-state concentrations obtained after 1 week of a 15 mg q12h regimen:

Under these assumptions, the population median  $CL/F$  is 49 L/h, with a median terminal half-life of approximately 10 h.  $C_{min}$  for 90% of the population (P5 to P95) is projected to range from 20 to 60 ng/mL. The projected average CYP2D6 EM/PM  $CL/F$  ratio for the simulation above was around 3:1, and the range in  $CL/F$  was 12 to 100 L/h).

### C. Plasma Protein Binding

The *in vitro* protein binding of [ $^3H$ ] A-429202 and [ $^{14}C$ ] ABT-594 were determined in rat, dog, ferret and human plasma using the ultracentrifugation technique. Results are summarized in Table 18.

Table 18. Protein Plasma Binding for A-429202 and ABT-594

A-Number	Rat Plasma (%)	Dog Plasma (%)	Ferret Plasma (%)	Human Plasma (%)
A-429202	24.5 $\pm$ 1.2	47.2 $\pm$ 1.1	38.1 $\pm$ 1.8	44.6 $\pm$ 1.8
ABT-594	51.7 $\pm$ 3.2	N.D.	34.0 $\pm$ 0.6	87.7 $\pm$ 0.2

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## XIV. Safety and Toxicology

A-429202 exhibited a wider therapeutic window relative to ABT-594 with respect to seizure threshold, effects on locomotor activity, body temperature, balance and coordination. The observed effects on locomotor activity, body temperature, balance and coordination that were observed fully attenuated upon repeated dosing, whereas under identical repeat administration protocols, analgesic efficacy was fully retained. A-429202 exhibited no effects on *in vitro* cardiac Purkinje fiber repolarization at concentrations up to 10-fold above a therapeutically effective plasma concentration, and a small (6.7%) change at 100-fold above therapeutic plasma concentrations. hERG channel activity at concentrations up to 100-fold above a therapeutically effective plasma concentration were not affected. A-429202 produced graded and self-limiting reductions in mean arterial pressure and cardiac contractile function in the anesthetized dog beginning at plasma concentrations of 13- and 56-fold above a therapeutically effective plasma concentration, respectively. No effects on QTc interval were observed up to 56-fold above a therapeutically effective plasma concentration. In the rat, at a dose 50-fold above a therapeutically effective dose, no effects on GI transit time were observed. At a dose 150-fold above a therapeutically effective dose, a 17% reduction in GI transit time was observed. A-429202 was neither mutagenic nor clastogenic when evaluated in genotoxicity assays. In a two-week toxicity study in rats, daily oral administration of A-429202 was well-tolerated at dosages up to 30 mg/kg/day as determined by clinical signs, body weight, food consumption, organ weights, gross necropsy, histopathologic evaluation of tissues, hematology and clinical chemistry measurements.

### A. CNS Safety

#### 1. LD<sub>50</sub> and Seizure Threshold in Mice

Groups of mice (five per group, dosed at 100, 200, 250, 300, 400 or 500  $\mu\text{mol/kg}$ , i.p.) were administered test compound and were observed for overt signs of seizures (myoclonus or tonic-clonic) for a period of at least 15 minutes. From the observations, ED<sub>50</sub> values for seizures and lethality were calculated. The results are summarized in Table 19.

Table 19. Acute toxicity of A-429202 and ABT-594 in the mouse.

	Seizure Threshold	LD <sub>50</sub>
A-429202	239.5	258.7
ABT-594	1.9	19.1

After compensating for the difference in potency of A-429202 and ABT-594 in efficacy models, the therapeutic index relative to lethality is comparable. However, approximately a 10-fold improvement in therapeutic index relative to seizure threshold is observed for A-429202.

#### 2. Effects on Locomotor Activity

Neuronal nicotinic receptor agonists, including ABT-594 and nicotine, exhibit a characteristic biphasic effect on motor activity, suppressing activity at early time points, and activating at later time points. A-429202, at 6.2  $\mu\text{mol/kg}$ , i.p., also displayed this effect on spontaneous motor activity upon acute administration. Upon repeated administration (5 days, BID administration) both the depressor and activating effects were abolished (Figure 44). Comparable results were previously observed with ABT-594 (0.19  $\mu\text{mol/kg}$ , i.p. acute and repeated dosing, data not shown), and in this regard A-429202 does not differ significantly from ABT-594. The retention of analgesic efficacy upon repeat administration and the full attenuation of motor effects under these conditions, suggest that it is unlikely that the analgesic effects of A-429202 are confounded by direct effects on locomotor activity.

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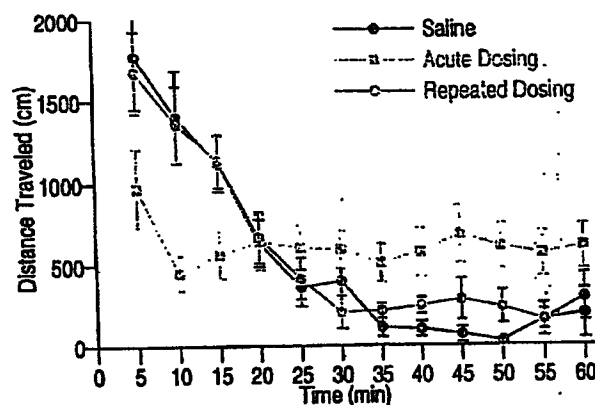


Figure 44. Effects of A-429202 on spontaneous motor activity in the rat after acute and repeated dosing.

### 3. Effects on Balance and Coordination: Rat Edge Test

A-429202 and ABT-594 were evaluated in the rat edge test, a measure of balance, motor coordination, and muscle strength (Figure 45, left panel). In this assay, the ability of rats to maintain balance on the edge of an open Plexiglas cube was measured, and reported as latency to fall relative to saline control. Both A-429202 and ABT-594 produced a dose-dependent decrease in latency time to fall, with ED<sub>50</sub> values of 4.4  $\mu\text{mol/kg}$ , i.p. and 0.08  $\mu\text{mol/kg}$ , i.p., respectively. This represents a 5-fold improvement in therapeutic index for A-429202 vs. ABT-594 relative to potency in the formalin pain assay, and a 3-fold improvement relative to the Chung neuropathic pain model.

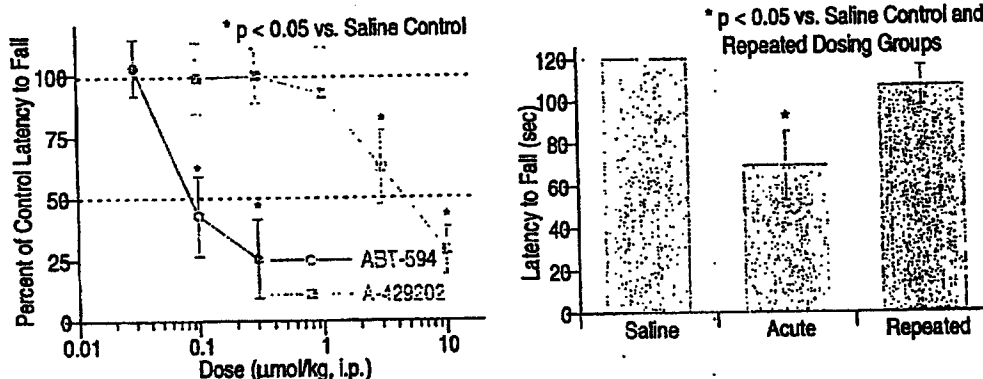


Figure 45. Evaluation of A-429202 in the Rat Edge Test model of balance and coordination after acute and repeated administration.

In a second experiment, A-429202 (6.2  $\mu\text{mol/kg}$ , i.p.) was administered to one group of rats twice daily for 5 days. A second group received saline until the second dosing period of the fifth day, at which point both groups received A-429202. The acute treatment group displayed the expected decrement in performance, whereas the repeat dosing group showed no significant difference from the saline control group (Figure 45, right panel). This contrasts the retention of analgesic efficacy under an identical repeat dosing protocol. ABT-594 (0.3  $\mu\text{mol/kg}$ , i.p.) had previously demonstrated a similar attenuation of impaired responding upon repeated dosing in this assay.

### 4 Effects on Balance and Coordination: Rat Rotarod

In the rat rotarod, an additional model of balance and motor coordination, acute administration of A-429202 (3, 6.2, and 10  $\mu\text{mol/kg}$ , i.p.) produced a small, but statistically significant decrease in latency to fall. At comparable multiples of a

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therapeutically effective dose, ABT-594 produced substantially greater deficits in this model (Figure 46, left panel). In a second experiment, rats were treated twice daily with either A-429202 (6.2  $\mu\text{mol/kg}$ , i.p.) or saline for 5 days, with all animals receiving active drug on the second dosing period of the last day. A similar magnitude of decrement was seen in the acute dosing group as had been previously observed in the acute dose-response study, but that effect did not reach statistical significance in this study. The repeat dosing group appears to have normalized to the saline control, but the failure of the acute dosing group to achieve statistical significance confounds the interpretation of this experiment (Figure 46, right panel).

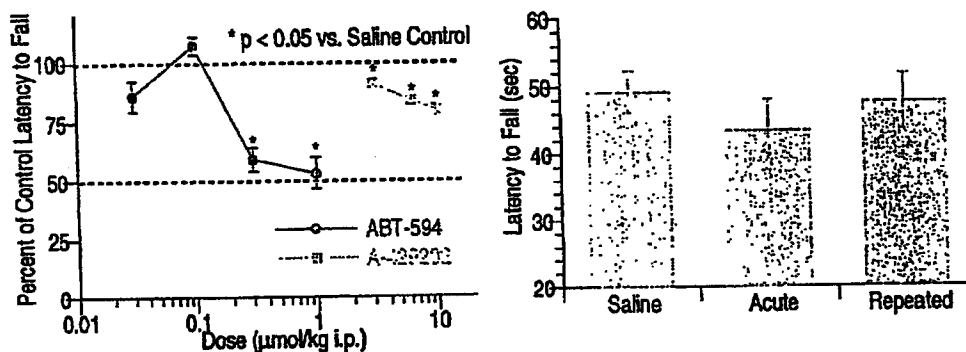


Figure 46. Evaluation of A-429202 in the Rat Rotarod model of balance and coordination after acute and repeated administration.

#### 5. Effects on Body Temperature

On acute administration in rats, A-429202 elicits a dose-dependent hypothermic response within the behaviorally relevant range (Figure 47, left panel). These results are consistent with the effects of other NNR agonists, including ABT-594. Upon repeated administration (6.2  $\mu\text{mol/kg}$ , i.p. BID, for 5 days) the effects fully attenuate (Figure 47, right panel). These data, along with the motor activity and motor coordination data, demonstrate that many of the side effect activities of A-429202 rapidly attenuate on repeat administration, while the analgesic efficacy is maintained.

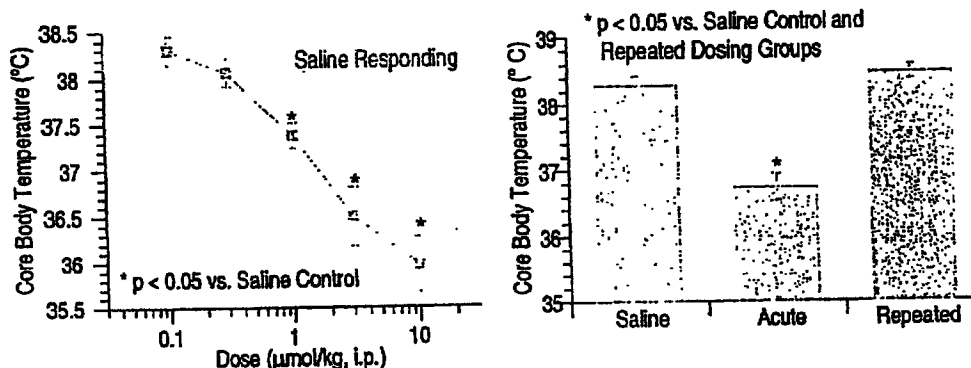


Figure 47. Evaluation of hypothermic effects of A-429202 in the rat after acute and repeated administration.

#### 6. Electroencephalography (EEG)

Slow wave EEG is present during periods of somnolence from drowsiness to very deep non-REM sleep. Slow waves can be indicative of a brain state in which processes associated with attention or vigilance are minimally functioning. The 1-4 Hz band, and its association with slow wave activity, allow for characterization of global stimulant or sedative

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actions of CNS drugs. A-429202 decreases slow wave EEG in a dose-dependent manner similarly to ABT-594, with approximately a 30-fold rightward shift of the dose-response curve (Figure 48). The effects are qualitatively similar to caffeine, and contrast the effects observed with morphine. These results are consistent with a mild stimulant effect, increased attention and vigilance, and suggest a lack of the sedative effects observed with opiates.

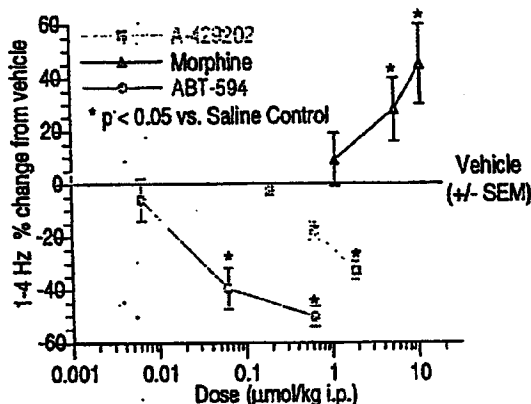


Figure 48. Evaluation of effects of A-429202, ABT-594, and morphine on slow-wave EEG as a model of attention and vigilance in rats.

## B. Cardiovascular Safety

### 1. *In Vitro* Effects on Cardiac Purkinje Fiber Repolarization

To evaluate the possible effects of A-429202 on ventricular repolarization, changes in action potential duration (APD) of canine cardiac Purkinje fibers were assessed *in vitro*. APD changes of isolated Purkinje fibers from adult beagle dogs were evaluated using standard microelectrode techniques and slow stimulation rates (30 beats per minute). The effects of A-429202 were examined at 10, 100 and 1000 ng/mL (or 1, 10 and 100 times the plasma concentration at ED<sub>50</sub> in the formalin model of 10 ng/mL) in comparison to vehicle controls ( $n = 6$  per group).

No significant prolongation (-0.23%) of the action potential duration was elicited at the anticipated therapeutic concentration (10 ng/mL). A higher concentration of A-429202 (100 ng/mL) also elicited minimal (1.17 %) prolongation of the action potential duration. Prolongation was modest but statistically significant (7.21%) at only the highest concentration tested (1000 ng/mL). For comparison, the APD prolongation for DMSO vehicle alone for these doses was -1.11, -1.05 and -1.73%, respectively. A-429202 did not exert any effects on the maximum upstroke velocity (an indication of cardiac fast inward sodium current) or resting membrane potential at any concentration tested. The extent of prolongation was far below the 15% prolongation value mentioned in previous draft regulatory guidelines for delayed repolarization. In summary, A-429202 does not significantly prolong repolarization of canine Purkinje fibers *in vitro* at concentrations equal to (and exceeding by at least 10 fold) the anticipated therapeutic concentration as predicted by preclinical models.

### 2. *In Vitro* Effect on hERG Current

The effect of A-429202 on *in vitro* hERG current was evaluated to assess the potential for delayed repolarization and prolongation of the QT interval. hERG (human-Ether-a-go-go-Related Gene) is a gene encoding the pore-forming subunit of a human delayed rectifier potassium channel, and blockade of hERG current is associated clinically with delayed repolarization and implicated in (and is a surrogate marker for) proarrhythmia with noncardiovascular drugs. In hERG-transfected HEK cells, A-429202 elicited minimal block of tail current amplitude (14% block [ $n = 3$ ] vs. 11% block with DMSO vehicle [ $n = 6$ ]) tested at a concentration of 1000 ng/mL. These results suggest minimal effects on cardiac repolarization with therapeutic concentrations of A-429202.

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### 3. Cardiovascular Evaluation of in the Anesthetized Dog

The cardiovascular response to intravenous administration of A-429202 was assessed using an anesthetized dog model (Dept. 46R). Beagles (9.1 – 12.4 kg, n=6/group, 2 groups) were anesthetized with sodium pentobarbital (35 mg/kg) and maintained (6 mg/kg/hr) at a surgical plane of anesthesia. Animals were intubated and mechanically ventilated. Electrocardiogram electrodes were placed in a lead II configuration. A Swan Ganz catheter was advanced into the pulmonary artery via the right jugular vein. A dual sensor micromanometer was placed into the left ventricle of the heart via the right carotid artery.

The three doses of active drug or vehicle (D5W) were administered as a series of three 30-minute intravenous infusions. Doses (8, 24 and 80  $\mu\text{g/kg/min}$  = 0.240, 0.720, 2.40 mg/kg) were chosen to achieve therapeutic and supratherapeutic plasma concentrations. Animals were monitored for 1 hour following administration of the highest dose. Blood samples were taken at time 0 and at 15-minute intervals for the duration of the protocol. Plasma samples were transferred to Dr. Kennan Marsh (D-4EK) for determination of blood concentrations of active drug.

In the anesthetized dog, administration of A-429202 at 0.240, 0.720, 2.40 mg/kg produced peak plasma concentrations of  $77 \pm 12$ ,  $284 \pm 44$  and  $874 \pm 125$  ng/mL. These concentrations are 5- to 58-fold greater than the estimated pre-clinical therapeutic concentration. At plasma concentrations up to  $77 \pm 12$  ng/mL (or 5-fold pre-clinical efficacious), A-429202 produced no physiologically significant effects in any parameter measured. As plasma levels increased to  $196 \pm 21$  ng/mL midway through the second dose, mean arterial pressure decreased to  $-13 \pm 4\%$  below baseline. Subsequently, mean arterial pressure decreased to  $-34 \pm 6\%$  and  $-39 \pm 4\%$  below baseline at the midpoint and end of the high dose infusion, respectively (plasma concentration =  $851 \pm 170$  and  $874 \pm 125$  ng/mL). Decreases in mean arterial pressure were associated with graded reductions in systemic vascular resistance. Heart rate decreased modestly to  $-15 \pm 4$  and  $-20 \pm 3\%$  below baseline during the high dose period, respectively. Sixty minutes after the infusion was terminated, heart rate remained  $-25 \pm 3\%$  below baseline. Indices of cardiac contractile function ( $dP/dt_{\text{max}}$  and  $dP/dt @ 50\text{mmHg}$ ) decreased at supratherapeutic plasma concentrations. Midway through the second dose  $dP/dt_{\text{max}}$  decreased to  $-32 \pm 9\%$  below baseline ( $196 \pm 21$  ng/mL);  $dP/dt_{\text{max}}$  decreased to  $-42 \pm 6\%$  below baseline at the end of the high dose infusion ( $874 \pm 125$  ng/mL). A-429202 produced no consistent change in the corrected QT interval (n=4). PR interval (n=5) increased modestly ( $9 \pm 1$  to  $14 \pm 1\%$ ) during the 60-minute post treatment period when reductions in heart rate were most pronounced.

The overall cardiovascular profile of A-429202 is consistent with that of ABT-594. With respect to ABT-594, throughout its clinical investigation, no clinically meaningful trends were observed for vital signs, physical exams or ECGs in any of the ABT-594 treated subjects. A-429202 produces graded reductions in mean arterial pressure and cardiac contractile function in the anesthetized dog beginning at plasma concentrations of  $196 \pm 12$  and  $851 \pm 44$  ng/mL, (13- and 56-fold efficacious), respectively.

### C. Renal Studies

Acute renal excretory function was assessed in conscious male Sprague Dawley rats (n=8/group; 7 groups). A-429202 was administered orally at 0, 2.4, 7.2, 24 and 72  $\mu\text{mol/kg}$  (0.75, 2.5, 7.5 & 25 mg/kg free base weight). Urinary excretion of fluid, sodium and potassium were determined over a five-hour period following treatment. Subsequently, terminal blood samples were collected for determination of plasma levels of A-429202. Hydrochlorothiazide (3.0 mg/kg, p.o.) was used as a diuretic standard. The effects of the vehicle control on urinary excretory function were assessed concurrently.

Oral administration of A-429202 to conscious rats produced no significant effect on acute urinary excretion of fluid, sodium or potassium at doses of 2.4 and 7.2  $\mu\text{mol/kg}$  (0.75 and 2.5 mg/kg). When administered at 24  $\mu\text{mol/kg}$  (7.5 mg/kg), A-429202 produced a modest increase in urinary excretion of fluid ( $59 \pm 15\%$ ) compared to vehicle control, but did not significantly alter renal excretion of sodium or potassium. The high dose (72  $\mu\text{mol/kg}$ ) increased urinary excretion of fluid ( $102 \pm 10\%$ ) sodium ( $184 \pm 16\%$ ) and potassium ( $91 \pm 19\%$ ). At 5.5 hours post dose, plasma concentrations of A-429202 were  $1.41 \pm 0.38$ ,  $3.31 \pm 0.50$ ,  $13.54 \pm 1.26$  and  $160.68 \pm 21.55$  ng/mL, respectively; based on the pharmacokinetic profile of A-429202, these values are consistent with  $C_{\text{max}}$  values of approximately 15, 45, 150 and 450 ng/mL. Therefore, these data suggest that A-429202 produces no effect on acute renal excretory function in the conscious rat at doses producing a  $C_{\text{max}}$  of 45 ng/mL (3-fold efficacious); at a  $C_{\text{max}}$  ten-fold therapeutic, the compound produces a modest diuresis with no effect on electrolyte excretion. Therefore, the acute renal excretory profile should not preclude further development of A-429202.

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#### D. Gastrointestinal Effects

Opioid therapy leads to decreased GI motility and constipation, and is one of the key adverse events associated with opioids responsible for discontinuation of therapy. In a rat model of GI motility, A-429202 had no significant effect on GI transit when dosed at either 30 or 100  $\mu\text{mol/kg}$ , and caused ~17% inhibition of transit at 300  $\mu\text{mol/kg}$  (Figure 49). Morphine sulfate (M. S.), administered at a dose known to produce constipation, inhibited transit by ~35%. The highest dose of A-429202.47 tested (300  $\mu\text{mol/kg}$ ) was approximately 150-fold above an effective oral dose in the rat formalin model of nociceptive pain, and resulted in an average plasma level (at 1.75 h post drug administration) of compound that was at least 6.5-fold greater than that deemed efficacious in a rat Chung model of neuropathic pain. Therefore, A-429202 would not be expected to have significant adverse effects on GI motility.

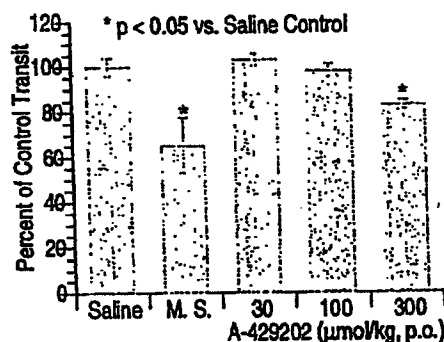


Figure 49. Effects of A-429202 on GI intestinal transit time as a model of constipation liability.

#### E. Genotoxicity

##### 1. Mutagenicity

A-429202 was evaluated in a bacterial reverse mutation screening assay for mutagenic activity (frameshift and base-pair substitution) measured by the ability of auxotrophic bacterial strains to grow in the presence of minimal histidine (Ames test)<sup>22</sup>. The mini-screen Ames test was conducted using *Salmonella typhimurium* strains TA98 and TA100 with 2 wells per treatment condition (vehicle and positive controls had three wells per treatment) in 6-well plates. All tests were conducted with and without Aroclor 1254-induced male rat liver microsome S-9 (metabolic) activation.

A-429202 (lot no. 695983) dissolved in DMSO was tested at 0.4, 1.2, 4, 12, 40, 120, 400, 800 or 2000  $\mu\text{g/well}$  in *Salmonella* strains TA98 and TA100. At all concentrations examined, A-429202.47 was non-mutagenic both in the presence and absence of metabolic activation as evidenced by the lack of concentration-related two-fold increases in mutant colonies over vehicle control. Furthermore, no toxicity was seen up to 2000  $\mu\text{g/well}$ .

##### 2. Clastogenicity

A-429202 was evaluated for its ability to induce chromosome damage using the Chinese hamster V79 lung cell *in vitro* micronucleus assay<sup>23</sup>. Micronuclei (MN) are small nuclear chromatin bodies arising either from DNA strand breaks or from spindle dysfunction and form as a consequence of mitosis. The cytokinesis blocking agent cytochalasin B is added to the cell culture medium to distinguish between cells which have undergone mitosis during the 16-hour course of the experiment and become binucleate from cells which have not undergone mitosis and remain mononucleate. Only binucleate cells are assessed for MN; the ratio of binucleate to mononucleate cells provides an indication of the compound effects on inhibition of cell proliferation.

A-429202 (lot no. 695983) dissolved in DMSO was tested at 10, 50, 100, 250, 500 or 1000  $\mu\text{g/mL}$ ; V79 cells were exposed for three hours in the presence or absence of S-9. 400 total cells were examined for toxicity and 600 binucleate cells were examined for micronuclei for each concentration evaluated. No toxicity was seen (no reduction in percents of binucleated cells at 1000  $\mu\text{g/mL}$ ) presence or absence of S-9. Therefore, A-429202 was considered non-clastogenic when tested up to 1000  $\mu\text{g/mL}$  in this assay.

#### F. Two-Week Oral Toxicity Study in Rats<sup>24</sup>

The toxicologic and pathologic effects of A-429202 were evaluated in Sprague Dawley rats (5/sex/group) following oral administration at dosages of 10, 30 and 60 mg base/kg/day for fourteen days. An additional 3 rats/sex/group were used for measurement of plasma concentration. Measured parameters included: clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology and plasma A-429202 levels.

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These dosages provided exposures, based on AUC, that were approximately 70-177 times higher than the exposures at the ED<sub>50</sub> in efficacy models.

Clinical signs considered significant were generally limited to the 60 mg base/kg/day group rats. These included decreased activity, rough hair coat, matted hair, emaciation, dehydration and green discoloration of urine. The green discoloration of urine was probably caused by presence of drug or metabolite, as there were no compelling clinical pathological, or gross or microscopic pathological evidence of liver, kidney or other organ dysfunction in these rats. This is currently being investigated. A statistically significant decrease in food consumption was observed throughout the study for all male rats that were treated with A-429202. However, a concomitant decrease in body weight was recorded throughout the study only for male rats administered 60 mg/kg/day of A-429202. Statistically significant decreases in food consumption were also observed during the first week of study for female rats that were treated with 30 or 60 mg/kg/day of A-429202. Concomitant decreases in body weights were recorded from Day 3 – Day 7, and Day 3 – Day 10, respectively, in these same (30 and 60 mg/kg/day) dosage groups.

Pharmacokinetic profile of A-429202 showed that there was adequate exposure of A-429202 in both male and female rats. AUC values tended to increase in a linear manner with increasing dosages on both Day 0 and Day 13. AUC values in the 10 and 30 mg/kg/day dose groups on Day 13 were 2211 and 4566 ng•hr/mL, respectively, and were similar to or slightly lower than those recorded on Day 0 (2099 and 5688 ng•hr/mL for 10 and 30 mg/kg/day dose groups, respectively). However, AUC values in the 60 mg/kg/day dose group were approximately 30% higher (11,695 ng•hr/mL) on Day 13 when compared to those obtained on Day 0 (8395 ng•hr/mL). No significant or consistent trends were noted in the data obtained from male vs. female rats in this study.

Changes in clinical pathology were limited to one rat in the 60 mg/kg/day group. These included a mild lymphocytopenia, a five-fold elevation in alanine aminotransferase, and a seven-fold elevation in bile acids. The lymphocytopenia may have been a reflection of endogenous corticosteroid-mediated (stress-related) decline in lymphocytes. The elevations observed with the leakage enzymes did not correlate with one another in any particular animal. The significance of these isolated events is unknown.

No drug-related tissue changes that were grossly visible during necropsy were reported. However, histologic evaluation of the tissues revealed lymphocytolysis in the thymus of one rat in the 60 mg/kg/day dose group, a change consistent with stress and lymphocytopenia earlier described.

In summary, 60 mg/kg/day of A-429202 was not well tolerated due to toxicological effects characterized by decreased food consumption with concomitant reduction in body weight, rough hair coat, emaciation, dehydration and elevations of liver enzymes. Therefore the no-observable- adverse-effect level (NOAEL) was determined to be 30 mg/kg/day.

## XV. Alternative Indications

### A. Depression

Recent research has suggested that NNR agonists may be useful for the treatment of depression, through their ability to modulate dopamine, serotonin and norepinephrine neurotransmitter systems in specific areas of the brain of relevance to depression, such as the prefrontal cortex, dorsal raphe and hippocampus<sup>25,26,27</sup>. Potentiation of dopaminergic neurotransmission in the prefrontal cortex and/or mesolimbic systems is a common response to treatment shared by a diverse array of antidepressants<sup>28</sup>. In addition, enhancement of serotonergic neurotransmission in the dorsal raphe and hippocampus is also strongly associated with antidepressive effects<sup>29</sup>. Several studies using animal models have revealed that NNR agonists can indeed demonstrate antidepressant effects<sup>30,31</sup>. Moreover, in a recent small clinical study transdermal nicotine was effective in reducing the Hamilton depression score and with a faster onset of action than current antidepressants on the market<sup>32</sup>. A-429202 was assayed in the

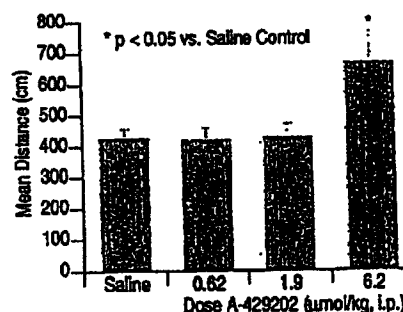


Figure 50. Reduction in enhanced immobility in mouse FST model of depression after treatment with A-429202.

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mouse forced swim test (FST), a validated model of depression primarily based on the despair experienced during the depressed state. A-429202, when injected i.p. at a dose of 6.2  $\mu\text{mol/kg}$ , showed a significant effect in reducing the enhanced immobility observed in mice in this model, as measured by distance swum in the FST (Figure 50). The magnitude of this effect is comparable to that obtained with A-85380 (a more potent NNR agonist) and with the TCA antidepressant amitriptyline, and is greater than that obtained with nicotine.

These findings suggest that A-429202 may also be useful for the treatment of depression. It is possible that these effects may be mediated, at least in part, through the ability of A-429202 to enhance dopamine release.

## B. Cognitive Impairment

The role of NNRs in cognitive function is well established, with the  $\alpha 4\beta 2$  receptor being perhaps one of the most implicated to play a significant role<sup>33</sup>. ABT-418 and (-)-nicotine have also demonstrated beneficial effects on cognitive function in humans, especially with respect to attention and vigilance<sup>33,34,35</sup>. These studies are supported by data from animal models.<sup>36</sup> NNR activation stimulates the release of several neurotransmitters prominently involved in cognition, such as dopamine, acetylcholine and norepinephrine<sup>37,38</sup>. Thus, it is possible that A-429202, which demonstrates an improved  $\alpha 4\beta 2$  NNR selectivity profile to ABT-418 and also demonstrates significant stimulation of dopamine release, may be beneficial for enhancement of cognitive function. Studies to assess the potential of A-429202 to reverse cognitive deficits are planned.

## C. Anxiety

There is evidence that nicotine or NNR agonists may show anxiolytic properties in specific animal models of anxiety<sup>34,39</sup>. A-429202 was assayed in the elevated plus maze (EPM) model of anxiety, a standard model in the field. A-429202, at doses of 0.62, 1.9 or 6.2  $\mu\text{mol/kg}$ , was ineffective in reducing anxiety via any of the specific measures in this assay.

## D. Schizophrenia

Schizophrenia is another neuropsychiatric disease, in addition to depression, where NNR agonists may prove therapeutically beneficial. Deficits in  $\alpha 4\beta 2$  have been demonstrated in schizophrenics in post-mortem studies<sup>40</sup>. Recently, nicotine has been found to selectively enhance dopamine levels in the prefrontal cortex over other dopaminergic areas of the brain and this enhancement appears to be mediated by the  $\alpha 4\beta 2$  receptor<sup>41</sup>. The Project has also demonstrated significant increase in dopamine release in the prefrontal cortex *in vitro* by nicotine or other NNR agonists<sup>18</sup>. Low dopaminergic activity in prefrontal cortex is correlated with cognitive, specifically working memory, deficits in schizophrenia<sup>42</sup> and an increase in dopamine levels in the prefrontal cortex has been shown to enhance working memory<sup>43</sup>. Thus, activation of the  $\alpha 4\beta 2$  NNR by A-429202 and/or its ability to enhance dopamine release may prove beneficial for schizophrenia. It should be noted that cognitive impairment is the primary factor determining prognosis in schizophrenia, an aspect of the disease not addressed by treatment with typical antipsychotics<sup>44</sup>.

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## XVI. Competition

## A. Within Project Approach

Compound	Mechanism of Action	Indication	Status	Additional Information
Altinicline (Eli Lilly/SIBIA)	NNR Agonist	Alzheimer's, Parkinson's, eating disorder, Alzheimer's, Schizophrenia, ADHD, Cognitive disorders, Depression, Pain.	Discontinued	Targets nAChR subtype modulators; Little information available on Altinicline's activities in pain, likely focusing on non-pain indications first; SIBIA is a subsidiary of Merck.
SIB-1553A (Eli Lilly/SIBIA)	NNR Ligand	Alzheimer's, Parkinson's, Neurological disorders.	Discontinued	Latest stage: PII on Alzheimer's.
GTS-21 (Taiho/Univ. of Florida)	NNR Agonist	Alzheimer's disease, schizophrenia	Discontinued	Phase I completed in UK; seeking a development partner to conduct Phase II trials in the US or EU.
CP-526,555 (Pfizer)	NNR $\alpha 4\beta 2$ partial agonist	Smoking cessation	Phase II	Strong signal reported in Phase II trial.
Trans-Metanicotine (RJR-2403) (Targacept/Aventis)	NNR Agonist	Alzheimer's, Pain, Dementia.	Phase I/suspended	The development was suspended by late 1999 due to a "use patent" problem, no recent development reported.
SIB-T1887 (SIBIA)	NNR Agonist	Pain	Pre-Clinical/Discontinued	No recent development reported.
AR-R-17779 (AstraZeneca)	NNR Agonist	Alzheimer's, Neurodegenerative disease, Anxiety disorder	Pre-clinical	No development activities in pain reported. Negligible CNS penetration (Abbott findings)
Liposome encapsulated (-)-Nicotine	NNR agonist Angiogenesis stimulant	Cardiovascular	Pre-Clinical	Stanford Univ.
Conotoxins (Univ. of Queensland)	NNR Antagonist	Pain, cerebrovascular ischemia, neurological disease	Discovery (Australia)	
Epibatidine analogs (Bayer)	NNR ligand	Pain	Discovery	

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**B. Within Therapeutic Area**

Compound	Mechanism of Action	Indication	Status	Additional Information
Prialt (ziconotide)	Blocker of neuronal N-type voltage-sensitive calcium channels	Neuropathic pain	Pre-registration/Phase III	Delivered via pump. Most likely will be used for patients with severe neuropathic pain. In Feb/02, FDA requested additional 18-month PIII studies; however, drug can be made available to patients for compassionate use.
Gabapentin	Unknown ( $\alpha 2\delta$ modulator?)	Neuropathic pain	Phase III	
Prebagalin	Unknown ( $\alpha 2\delta$ modulator?)	Neuropathic pain	Phase III	
Clonidine Gel	$\alpha 2$ adrenergic agonist	Neuropathic pain	Phase III	
Harkoseride (ADD234037)		Neuropathic pain	Phase II	
CNS 5161	NMDA antagonist	Neuropathic pain	Phase II	
Colykade	Cholecystokinin B (CCKB) receptor antagonist	Neuropathic pain	Phase II	To be used in combo with morphine and unlikely to play major role in NeP market.
Devacade	Selective cholecystokinin A (CCKA) receptor antagonist	Neuropathic pain	Phase II	To be used in combo with morphine and unlikely to play major role in NeP market.
Neurodex (dextromethorphan)	NMDA antagonist	Neuropathic pain Diabetic neuropathy Post herpetic neuralgia	Phase II	
memantine	NMDA antagonist	Neuropathic pain Diabetic neuropathy	Phase II	
resiniferatoxin	Vanilloid	Neuropathic pain	Phase II	
ZD 6416	Prostaglandin endoperoxide 1 antagonist	Neuropathic pain	Phase II	
R-ketoprofen	R-(-)-enantiomer of ketoprofen	Neuropathic pain	Phase II	
JTC801	4-aminoquinoline derivative and novel nociceptive antagonist	Pain Diabetic complications	Phase I	Japan Tobacco
CHF-3381	Monoamine oxidase A inhibitor, Monoamine oxidase B inhibitor, NMDA antagonist.	Neuropathic Pain Epilepsy Parkinson's Alzheimer's	Phase I	Chiesi (Italy)
GPI 5693	N-acetylated-alpha-linked acidic dipeptidase	Diabetic neuropathy Neuropathic pain	Phase I	Guilford Pharm
GW 493838	Adenosine A1 receptor antagonist	Neuropathic pain	Phase I	GSK
CI 1041	NMDA antagonist	Neuropathic pain	Phase I	Purdue Pharma/Pfizer
NGX 4010		Neuropathic pain	Phase I	NeurogesX
GPI 5000	N-acetylated-a-linked acidic dipeptidase (NAALADase) inhibitor	Diabetic neuropathy Neuropathic pain	Preclinical	

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### C. Competitive Analysis

**Within Project Approach:** Interest and competition in NNRs continues to build. Major competitors with Research and Development efforts targeting NNR ligands include: Eli Lilly, SIBIA/Merck, Pfizer, Targacept (R. J. Reynolds), Taiho, Bayer, and Research Triangle Institute. Most companies that are active in the area are believed to have programs targeting the analgesic aspects of NNRs. In addition, these compounds also target neurodegenerative diseases such as Alzheimer's disease, dementia, cognitive disorders, and Parkinson's disease. It appears at this point that no compounds from the NNR class targeting pain have passed through Phase I, and A-429202 could be one of the first NNR compounds to obtain a pain indication.

**Neuropathic Pain:** Numerous programs with diverse approaches are in development targeting a neuropathic pain indication, some of which also intend to treat the underlying disease state (e.g., diabetic neuropathy). Beyond Neurontin, there has been little clinical success with novel agents so far, and Pfizer will likely continue to play a key role in driving the growth and shaping the market with anticipated approvals of Neurontin and pregabalin in neuropathic pain. The first to market with a competitive profile (vs. Neurontin/pregabalin) may reap large rewards.

**Nociceptive Pain:** There are over 200 development programs targeting nociceptive pain. The majority of compounds in the pipeline represent incremental improvements to the opioids or NSAIDs/COX-2's, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 40% of the compounds in development are novel compounds with unique mechanisms of action. These novel mechanisms are expected to post the real competition for A-429202. Selected compounds in development are listed in Appendix B, and major approaches include:

- Opioids/NSAIDs/COX-2's, including new formulations and delivery mechanisms.
- Cholinergic channel modulators (please refer to "Within Project Approach" section).
- Calcium channel blockers: blocks N-type calcium channels and disrupts the pre-synaptic release of neurotransmitters and neuropeptides that transmit inter-synaptic pain signals.
- Selective neuronal sodium channel antagonists: expressed exclusively in small sensory neurons thought to be related to the central sensitization in chronic pain.
- GABA modulators: binds GABA and is the principle mediator of inhibitory neurotransmission in the brain.
- NMDA receptor antagonists: such as dextromethorphan, can suppress central sensitization. NMDA-receptor activation not only increases the cell's response to pain stimuli, it also decreases neuronal sensitivity to opioid receptor agonists.
- Neurokinin antagonists: antagonists of three related peptide neurotransmitters, substance P, neurokinin A and neurokinin B, have shown analgesia effects.
- Prostaglandin E (PGE) modulators

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## XVII. Follow-On Strategy

The strategy of the project team is to identify a second compound with a comparable profile to A-429202, but structurally distinct and derived from a separate chemical series. To date, the most promising and most fully characterized lead is A-422894. This compound exhibits a comparable *in vitro* profile to A-429202, is active in models of nociceptive and neuropathic pain, and exhibits a comparable therapeutic index to A-429202 relative to emesis liability. It differs from A-429202 in several significant ways. A-422894 exhibits greater potency in neuropathic pain and lesser potency in nociceptive pain models relative to A-429202, and it exhibits a longer half-life in rat. Relative to emesis liability in the ferret model, A-422894 and A-429202 are comparable.

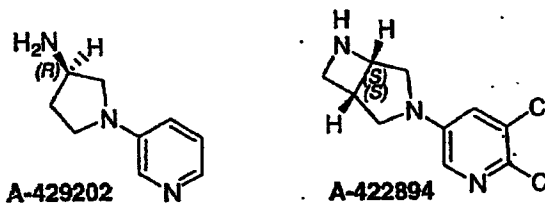


Figure 51. Chemical structures of A-429202 and A-422894.

### A. *In Vitro* Activity

A-422894 can be viewed as a 3-aminopyrrolidine embedded within the 3,6-diazabicyclo[3.2.0]heptane core. Compared to 429202, A-422894 shows similar affinity to the cytosine ( $\alpha\beta 2$ ) binding site in rat brain membranes ( $K_i = 0.18$  nM); it is a full agonist at recombinant human  $\alpha\beta 2$  and  $\alpha\beta 4$  subtypes, with comparable potency but a slightly lower level of *in vitro* selectivity versus A-429202 (Figure 52).

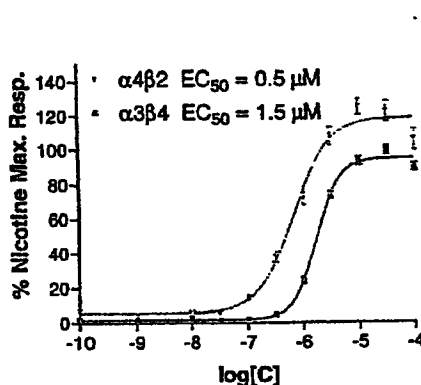


Figure 52. *In vitro* functional profile of A-422894 at the  $\alpha\beta 2$  and  $\alpha\beta 4$  NNR subtypes.

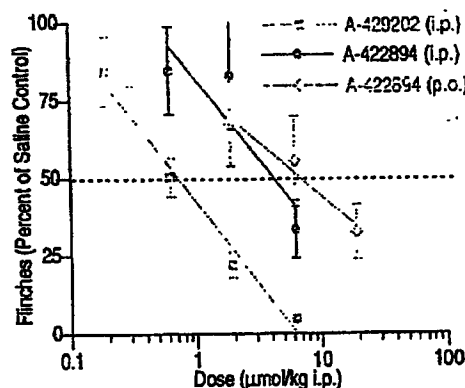


Figure 53. Comparison of efficacy and potency of A-422894 to A-429202 after i.p. and oral administration in the formalin model of persistent nociceptive pain.

### B. *In Vivo* Activity

In the rat formalin model of persistent nociceptive pain, A-422894 exhibited a significant analgesic effect following an ip dose of  $6.2 \mu\text{mol/kg}$ , but full efficacy was not reached even at a dose of  $19 \mu\text{mol/kg}$ . The apparent  $ED_{50}$  is  $4 \mu\text{mol/kg}$ , and on this basis A-422894 is approximately 5-fold less potent than A-429202. Comparable analgesic activity followed oral administration, albeit with a small rightward shift of the dose-response curve (Figure 53). A nicotinic mechanism of action was indicated by the fact that the antinociceptive effect of A-422894 ( $19 \mu\text{mol/kg}$ , ip) was completely blocked by the NNR antagonist mecamylamine (data not shown).

A-422894 was particularly effective in the Chung model of nerve injury-induced neuropathic pain. Figure 54 (left panel) illustrates the comparison of dose-response curves for A-422894 and A-429202 based on the antialodynic effect at the 15-minute time point. It can be seen that A-422894, with an  $ED_{50}$  of  $1.0 \mu\text{mol/kg}$ , is roughly twice as potent as 429202.

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Moreover, A-422894 produced a longer-lasting effect than does A-429202. As shown in Figure 54 (right panel), an i.p. dose of 6.2  $\mu\text{mol/kg}$  of A-422894 resulted in a fully efficacious response that retained significant activity one hour after dosing. The persistent effect following the dose at 19  $\mu\text{mol/kg}$ , i.p. (lasting 2 h) was completely blocked by pretreatment with the NNR antagonist mecamylamine, confirming the nicotinic mechanism for this response (data not shown).

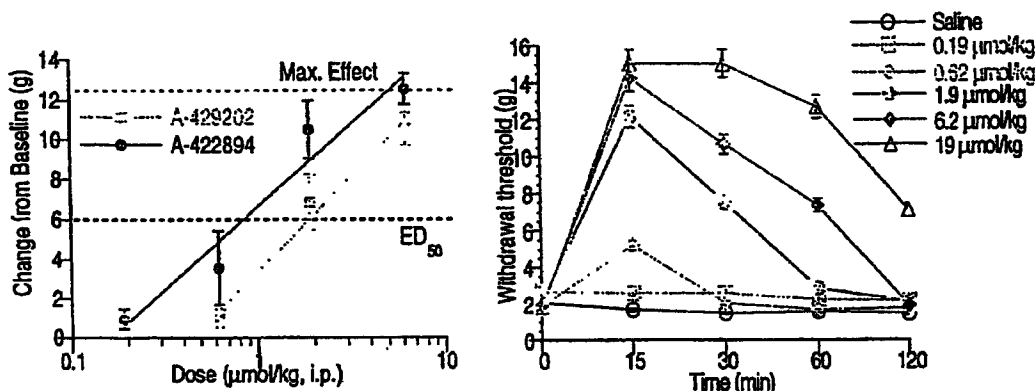


Figure 54. Evaluation of maximal effect and duration of action of A-422894 in the Chung model of neuropathic pain

Emesis results for acute (i.p.) dosing of A-422894 in the ferret are shown in Figure 55. No emesis was observed at 1  $\mu\text{mol/kg}$ , with higher doses causing increased percentage of animals experiencing emesis. Overall, the emesis dose-response curve for A-422894 is quite similar to that for A-429202. Likewise, the number and severity of emetic events was relatively small, reflected in the emesis index values that remained low even at the high end of the dose-response curve. Based on an estimated  $\text{ED}_{50} = 1.0 \mu\text{mol/kg}$  for Chung, the therapeutic plasma concentration is approximately 34 ng/mL. The equivalent-dose exposure in a ferret was significantly larger, reaching  $C_{\text{max}} = 85 \text{ ng/mL}$  following a dose of 1  $\mu\text{mol/kg}$ , i.p. Based on this plasma level analysis, the therapeutic index for A-422894 (Chung model vs. emesis in ferret) is approximately 10, similar to the value derived for A-429202.

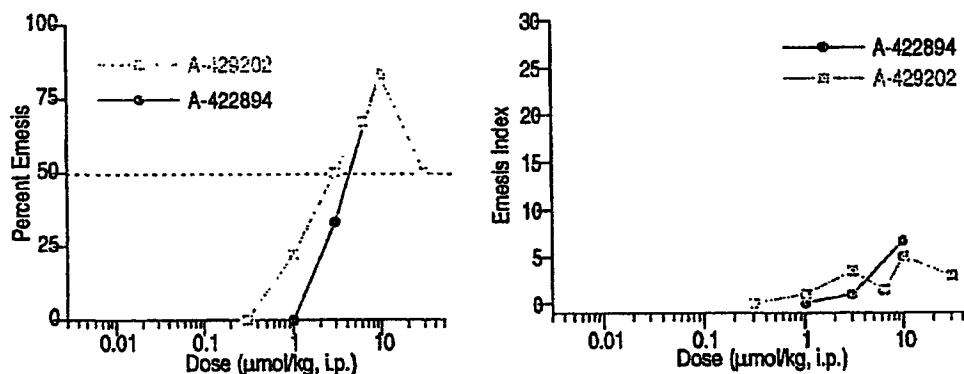


Figure 55. Comparison of the emesis liability of A-422894 and A-429202 in the ferret model.

As with A-429202, the emetic effects of A-422894 diminished with the repeated dosing schedule. Figure 56 displays results from five day, twice daily dosing of A-422894; emesis from the morning dosing period are compared to A-429202. Whereas an acute dose of A-422894 at 6.2  $\mu\text{mol/kg}$  caused emesis in 50% of the animals, the effect tolerated quickly. Nausea behaviors similarly declined as had previously been observed with A-429202 (data not shown).

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Preliminary pharmacokinetic evaluation of A-422894 in rat indicates that the compound is efficiently absorbed ( $F = 86\%$  and  $57\%$  for ip, po administration, respectively) with moderate clearance ( $1.3 \text{ L/h/kg}$ ). The plasma level following an i.p. dose of  $1.9 \mu\text{mol/kg}$  reached  $C_{\text{max}} = 64 \text{ ng/mL}$ , and decayed with a terminal half-life of  $1.8 \text{ h}$ .

Based on these promising *in vivo* results for A-422894, the project has submitted the compound for evaluation in key studies of acute toxicity and ancillary pharmacology. Seizure threshold in mice for A-422894 has been evaluated, and only at high doses ( $\geq 500 \mu\text{mol/kg}$ , ip) were seizures observed. The estimated  $\text{ED}_{50}$  for seizure in this model is  $750 \mu\text{mol/kg}$ , and the acute lethal dose is approximately  $800 \mu\text{mol/kg}$ . Indexed to activity in the Chung model of neuropathic pain, this represents an approximate 4-fold improvement in therapeutic window.

Some preliminary studies have been initiated to assess the cardiovascular effects, especially on QT interval, of A-422894. The compound causes a concentration-dependent increase in action potential duration (APD) in canine Purkinje fibers, reaching  $4.4\%$  and  $23\%$  prolongation at concentrations of A-422894 corresponding to 10- and 100-fold above the therapeutic plasma level, respectively. Full hemodynamic evaluation of A-422894 in anesthetized dog is planned.

At the broad range of ion channels, GPCRs, neurotransmitter uptake sites, and enzyme systems evaluated in the CEREP screen, A-422894 was found to have significant ( $>50\%$  inhibition at  $10 \mu\text{M}$ ) affinity only at the sigma ( $77\%$  inhibition) and  $5\text{HT}_3$  ( $72\%$  inhibition) receptors.

In the mini-Ames screen (Study TX02-035), A-422894 was found to be non-mutagenic in *Salmonella typhimurium* (strains TA98 and TA100) at concentrations up to  $2000 \mu\text{g/well}$ , with and without rat liver metabolic activation (S-9). No toxicity, evidenced by reduced numbers of colonies, was seen at the highest concentration. Likewise, in the micronucleus assay (Study TX02-036), A-422894 was non-clastogenic to V79 cells, with and without S-9 activation.

In summary, A-422894 has been identified as an NNR-based analgesic with particular efficacy in a model of neuropathic pain and relatively low emetic liability. Among several key experiments, the success of A-422894 will depend on favorable cardiovascular evaluation in the anesthetized dog, demonstration that the analgesic effects are sustained through repeat dosing paradigms, a clean toxicology profile, as well as a prediction of acceptable pharmacokinetics in humans.

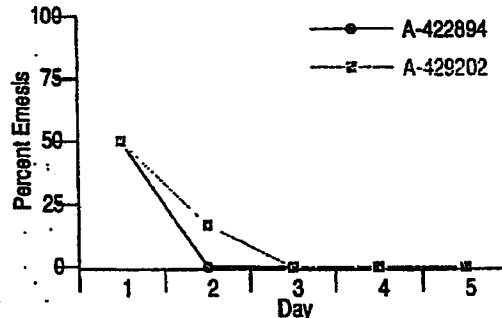


Figure 56. Evaluation of emetic liability of A-422894 after repeat dosing in the ferret model. Responses at AM dosing periods shown.

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## XVIII. Assessment of Opportunities and Risks

The development program for A-429202 will include both opportunities and risks. Several of those items are listed below.

### A. Opportunities

- A-429202 exhibits comparable efficacy and a significantly improved therapeutic index in preclinical models relative to ABT-594, the first compound from the NNR class to exhibit efficacy in the treatment of neuropathic pain.
- A-429202 may provide an additional therapeutic option for the substantial unmet medical need of patients suffering from neuropathic pain. Equivalent efficacy to gabapentin with a very low adverse event incidence, or greater efficacy with an acceptable level of adverse events may be achievable with this compound. No medication is currently approved in the US for this pain condition.
- The efficacy of the NNR pharmacology in the treatment of moderate to severe chronic nociceptive pain remains untested. A-429202 may be able to achieve opioid-like efficacy, while avoiding scheduling, development of tolerance, addiction liability, respiratory depression, and constipation liability associated with opiate therapy.
- A-429202 may provide a first in class treatment for pain, as well as serve as a target of further evaluation in treating other CNS disease states or conditions such as cognitive disorders (including Alzheimer's, mild cognitive impairment, ADHD, cognitive deficits associated with schizophrenia), depression, smoking cessation.
- A-429202 could be used in combination with opioids or other analgesics to provide greater efficacy, faster onset, or opioid-sparing effects. A combination formulation strategy could be used to manage the life cycle of this compound class.

### B. Risks

- The NNRs may be closely scrutinized for signs of physical addiction by regulatory agencies because of their close association with nicotine.
- Initiation of therapy may require a titration schedule to minimize the occurrence of side effects, which would adversely affect the usefulness in the treatment of pain associated with osteoarthritis. Dose titration is well accepted in the treatment of neuropathic pain.
- Commercial success requires no more frequent than a BID dosing regimen. A human half-life of significantly shorter than 6 hours could jeopardize achieving this requirement.
- The dependence of metabolism of A-429202 on a single CYP isoform may result in large differences in drug exposure between normal and poor metabolizers; CYP2D6 inhibitors (such as fluoxetine) may significantly affect clearance of A-429202.
- Clinical development of ABT-594 was discontinued due to an unacceptable emesis profile and delayed onset of activity. Well-defined Go/No Go criteria for the clinical evaluation of A-429202 will be necessary to continue development.
- Previous IND correspondence for ABT-594 concluded with FDA comments regarding concern over an ABT-594 subject who experienced third degree AV block, syncope, and orthostasis. FDA has requested that Abbott contact FDA prior to conducting any further investigations with ABT-594. The impact of this on the development of A-429202 is unclear. If the initial A-429202 study were to be done under an IND, development timelines would need to be extended.

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## XIX. Transition Team Goals

The goal of the Transition Team development program will be to A) establish whether the pharmacokinetics of A-429202 are consistent with BID dosing; B) evaluate tolerability at a target plasma concentration of 10 to 30 ng/mL that has been defined by the preclinical experiments as an efficacious plasma concentration; and C) evaluate the effects of various pharmacokinetic parameters on tolerability (in particular the effects of rate of rise on emesis and nausea). To meet these goals, the Transition Team envisions the use of both oral capsule and parenteral dosage forms. This will allow determination of absolute bioavailability, development of an optimal PK profile to minimize GI-related adverse events, and elimination of the uncertainty brought about by the significant difference in tolerability between oral solution dosing and capsule dosing encountered during the development of ABT-594.

### A. Clinical Development Plan

The clinical development plan will support a chronic pain indication using an oral dosage form. "Chronic" pain is any pain requiring >7 days treatment. Studies proposed to evaluate chronic pain will address both neuropathic and nociceptive pain states.

### B. Transition Team Strategy

Upon successful completion of the necessary toxicology studies and development of oral capsule and intravenous (parenteral) formulations, the Transition Team will conduct a Phase I study in healthy human volunteers. The objectives of this study are to determine the safety, tolerability, maximum tolerated dose, and pharmacokinetics of single oral and intravenous doses of A-429202. The first time in human study will be a randomized, double-blind, placebo-controlled, crossover, single-center, single rising dose study involving approximately 106 healthy adult subjects. This study will also include an evaluation of food and gender effects of A-429202, a sufficiently broad range in ages to assess kinetic dependency on renal function and a detailed assessment of cardiovascular behavior. All potential subjects will be genotyped for a panel of CYP2D6 alleles, with stratification and enrichment to address the issue of the magnitude of the EM/PM clearance ratio. If appropriate pharmacokinetic characteristics are demonstrated, and pre-clinical data are supportive, the team will proceed with a second Phase I study to determine the safety, tolerability and pharmacokinetics of ascending twice daily doses of an oral formulation of A-429202 in healthy adult subjects. Additional Phase I studies will include a CYP2D6 anti-depressant drug interaction study. Early assessment of <sup>14</sup>C metabolism, formulation refinement and interaction with CYP2D6 antidepressants during Phase I studies will be considered prior to initiating Phase II evaluation.

To demonstrate proof of concept for analgesic activity, a study will be conducted in patients with neuropathic pain. This phase II, randomized, double-blind, placebo-controlled, multicenter study will compare the safety and efficacy of multiple twice daily (BID) oral doses of A-429202 and placebo in patients with painful diabetic neuropathy. A provisional timeline for the development of A-429202 is outlined below.

This timeline assumes the following:

- Program funding is available immediately following the DDC review
- Bulk drug synthesis, one month toxicology studies, formulation development and stability testing are completed in time to deliver clinical supplies by 6/03
- The first single-dose study will be conducted as a non-IND, ex-US study.

Investigator Brochure	04/03
Clinical Protocol (Single-Dose)	04/03
IRB Approval	06/03
Start Dosing	07/03
End Dosing (8 groups)	11/03
Plasma Assays Complete	12/03
Preliminary PK Report	01/04
Go / No Go Decision	01/04
Completion of Clinical Supplies Reformulation	07/04

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File IND	09/04
Start Additional Phase I Studies (Multiple-dose, drug interaction, and absolute bioavailability)	10/04
Go / No Go Decision	04/05
Start Phase II Neuropathic Pain Study	07/05
Complete Neuropathic Pain Study	06/06

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**Appendix A – Diabetic Neuropathy Pipeline**

Compound	Mechanism of Action	Indication	Status	Additional Information
Aldos (fidarestat)	aldose reductase inhibitor	Diabetic neuropathy	Registration	Near term impact on global market will be small
Neurodex (dextromethorphan)	NMDA antagonist	Neuropathic pain Diabetic neuropathy Post herpetic neuralgia	Phase II	
memantine	NMDA antagonist	Diabetic neuropathy	Phase II	
pimagedine		Diabetic neuropathy	Phase II	
bimoclomol		Diabetic neuropathy	Phase II	
ReN1889		Diabetic neuropathy	Phase II	
POL 255		Diabetic neuropathy	Phase II	
GPI 5693	N-acetylated-alpha-linked acidic dipeptidase	Diabetic neuropathy Neuropathic pain	Phase I	
BRX-220		Diabetic neuropathy	Preclinical	
FK508 analogue		Peripheral Neuropathy	Preclinical	
prosaptide	Undefined	Diabetic neuropathy	Preclinical	
Pyridorin	Advanced glycation end product inhibitors	Diabetic neuropathy	Preclinical	
SG 210		Diabetic neuropathy	Preclinical	
ST 1211		Diabetic neuropathy	Preclinical	
Y 128		Diabetic neuropathy	Preclinical	
GPI 5000	N-acetylated-a-linked acidic dipeptidase (NAALADase) inhibitor	Diabetic neuropathy Neuropathic pain	Preclinical	

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**Appendix B – Selected Nociceptive Pain Pipeline by Mechanism of Action**

<b>NSAID, Opioid, and Opioid Combination</b>					
<b>Compound</b>	<b>Mechanism of Action</b>	<b>Indication</b>	<b>Status</b>	<b>Launch</b>	<b>Additional Information</b>
Arcoxia (Merck)	COX-2 inhibitor	Pain, inflammation	Pre-registration in US; approved in UK	After 2004	NDA withdrawn in March/02; Re-file expected in 6-10 months in US; approved in UK
parecoxib (Pharmacia)	COX-2 inhibitor	Pain, inflammation	Pre-registration in US; approved in EU	After 2005	Injectable; US NDA rejected; EU approved.
Oxyprofen (Forest)	Opioid combination	Pain, inflammation	Pre-registration	2003-2004	Oxycodone and ibuprofen combination
ADL 8-2698 (Adolor)	Opioid receptor antagonist	Pain, inflammation	Phase III		
COX-189 (Novartis)	COX-2 inhibitor	Pain, inflammation	Phase III		
tilmcoxib (Japan Tobacco)	COX-2 inhibitor	Pain, inflammation	Phase III/Japan		
BMS-347070	COX-2 inhibitor	Pain, inflammation	Phase II/III		
ML-3000	COX-2 inhibitor	Pain, inflammation	Phase II Discontinued		
AERx PMS (Aradigm)	Morphine	Pain	Phase IIb		Inhaled morphine device
PTI-555 (Pain Therapeutics)	Opioid	Pain	Phase II		Morphine/naltrexone combination
PTI-801 (Pain Therapeutics)	Opioid	Pain	Phase II		Novel formulation of oxycodone
ADL 2-1294 (Adolor)	Topical agent	Pain	Phase II		Topical agent for ophthalmic pain
ADL 10-0101 (Adolor)	Opioid	Pain	Phase II		System-selective opioid antagonist
dextro-methorphan comb (Endo)	Opioid agonist Prostaglandin synthase inhibitor NMDA antagonist	Pain	Phase II		Angiogenix
Opioid kappa receptor agonist (Adolor)	sufentanil, DUROS	Pain	Phase I		
<b>Cholinergic Channel Modulator</b>					
<b>Compound</b>	<b>Mechanism of Action</b>	<b>Indication</b>	<b>Status</b>	<b>Launch</b>	<b>Additional Information</b>
Liposome encapsulated (-)-Nicotine	Nicotinic agonist Angiogenesis stimulant	Cardiovascular	Pre-Clinical		
Aliticine (Eli Lilly/Merck)	Nicotinic ACh Agonist	Pain, eating disorder, Alzheimer's, Schizophrenia, ADHD, Depression.	Discovery		Targets nAChR subtype modulators.
Conotoxins (Univ. of Queensland)	Nicotinic ACh Antagonist	Pain, cerebrovascular ischemia, neurological disease	Discovery (Australia)		
Epibatidine analogs (Bayer)	Nicotinic ACh ligand	Pain	Discovery		

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GABA Modulator					
Compound	Mechanism of Action	Indication	Status	Launch	Additional Information
Gabapentin (Pfizer)	Calcium channel blocker	Epilepsy, neuropathic pain	Registered, Phase III	NeP in US after 2003.	
Pregabalin	Calcium channel blocker	Epilepsy, neuropathic pain	Phase III	2003-2004	
ganaxolone (CoCensys)	GABA agonist	Epilepsy, migraine, pain	Phase II		
Rufinamide (Novartis)	GABA B antagonist	Epilepsy, pain	Phase II		
CGP-35024 (Novartis)	GABA B agonist	Pain	Discovery		
NS-2979 (NeuroScience)	GABA modulator	Pain	Discovery		
Calcium Channel Blocker					
Compound	Mechanism of Action	Indication	Status	Launch	Additional Information
Ziconotide (SNX-111)	Calcium channel blocker, N-type	Neuropathic pain, Malignant pain, CNS	Pre-registration; Phase III	After 2004	In Feb/02, FDA requested additional 18-month PIII studies; however, drug can be made available to patients for compassionate use.
GABA pentinoid (Jouveinal)	Calcium channel blocker	Neuropathic Pain, IBS	Discovery		
PD-029361 (Pfizer)	Calcium channel blocker	Pain, brain injury	Discovery		
PD-157667 (Pfizer)	Calcium channel blocker	Pain, cerebrovascular ischemia	Discovery		
PD-158143 (Pfizer)	Calcium channel blocker	Pain, cerebrovascular ischemia	Discovery		
PD-158143 (Pfizer/Elan)	Calcium channel blocker, N-type	Pain,	Discovery		
VGCC antagonist (Eli Lilly/Merck)	Calcium channel blocker	Pain, cerebrovascular ischemia	Discovery		Voltage-gated calcium channels.
Neurokinin Antagonist					
Compound	Mechanism of Action	Indication	Status	Launch	Additional Information
SR-48968 (Sanofi)	Neurokinin antagonist	Pain, depression	Phase II		
L-758298 (Merck)	NK1 antagonist	Pain, emesis, inflammation	Phase I		
L-659877 (Merck)	NK2 antagonist	Pain	Discovery		
R-116301 (JNJ)	NK1 antagonist	Pain	Discovery		
PD-154075 (Pfizer)	NK1 antagonist	Pain, emesis, inflammation	Discovery		
Senktide (GSK)	NK3 agonist	Pain	Discovery		
SR-144190 (Sanofi)	NK2 antagonist	Pain, IBS, CNS	Discovery		
Win-51708 (Sanofi)	NK1 antagonist	Pain	Discovery		

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NMDA Receptor Antagonist					
Compound	Mechanism of Action	Indication	Status	Launch	Additional Information
Memantine (Forest/Merz)	NMDA receptor antagonist	Nociceptive pain, neuropathic pain, CNS disorder	Phase II	2005	
MRZ-2/579 (Merz)	NMDA receptor antagonist	Pain, CNS disorder	Phase I		
MPEP (Merck/Novartis)	NMDA receptor antagonist	Pain, CNS disorder	Discovery		
PD-196860 (CoCensys/Pfizer)	NMDA receptor antagonist	Pain, CNS disorder	Discovery		
CHF-3381 (Chiesi)	NMDA antagonist/MAO A&B inhibitor	Epilepsy, pain, CNS disorder	Discovery		
oral glycine (AstraZeneca)	NMDA receptor antagonist	Neuropathic pain	Discovery		
PGE Receptor					
Compound	Mechanism of Action	Indication	Status	Launch	Additional Information
Limprost (Ono)b	PGE1 agonist	Pain	Pre-registration (Japan)	2003	
SC-56551 (Merck Frost)	PGE1 agonist	Pain	Clinical		
PGE2 antagonist (AstraZeneca)	PGE2 antagonist	Pain, inflammation	Discovery		
ONO-NY-012 (Ono)	EP3 agonist	Pain, inflammation	Discovery		
Sodium Channel Blocker					
Compound	Mechanism of Action	Indication	Status	Launch	Additional Information
LTA (AstraZeneca)	Sodium channel blocker	Pain	Phase II		
QX-314	Sodium channel blocker	Pain	Discovery		
Conopeptides (Cognetix/StemCells)	Sodium channel blocker	Epilepsy, pain, CNS disorder	Discovery		
NW-1029 (Newron)	Sodium channel blocker	Pain	Discovery		
Co-102862 (CoCensys)	Sodium channel blocker	Epilepsy, Pain	Discovery		
BIII-890-CL (BI)	Sodium channel blocker	Epilepsy, Pain	Discovery		
Safinamide (Newron)	Sodium channel blocker	Epilepsy, pain, CNS disorder	Discovery		

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INTEROFFICE CORRESPONDENCE

FROM: Michael D. Meyer, Ph.D.  
 Senior Project Leader  
 NNR Project  
 DEPT. 47W BLDG. AP9A EXT 7-0338

TO:

DATE: May 17, 2002

Dan W Norbeck	R473	AP9-1	Ronald K Lloyd	06WP	AP34-3
John M Leonard	R432	AP9-1	Thomas J Lyons	0404	AP9-1
Jeff M Leiden	03RD	AP6D-2	Kennan C Marsh	04EK	AP9
Alejandro A Aruffo	RD22	Worcester	Heather L Mason	0533	AP30
Walid Awni	04PK	AP13A	Bruce McCarthy	R-48Q	AP34
John F Bauer	04P2	NCR13-3	Charles McLeskey	096R	LFCP4-4
Jorge D Brioni	R4ND	AP9A-3	Nicole Mowad-Nassar	096F	LFCP4
William H Bunnelle	R47W	AP9A-1	Chudy Nduaka	R4TD	AP13A-3
Shing Chang	0466	AP52-N-1	Terry J Opgenorth	04MA	AP10-1
Laurie B Corsi	042M	AP9A	Reid Patterson	046G	AP13A
Bryan F Cox	R-46R	AP9	Blasine Penkowski	D-533	AP30
Michael W Decker	R4N5	AP9A-3	Glenn A Reinhart	R46R	AP9
Tawakol A El-Shourbagy	046W	AP9	Friedrich W Richter	R434	AP9
Connie Faltynek	R4PM	AP9A-3	Stanley A Roberts	R46V	AP9-1
Steve Fesik	0460	AP10-LL	Lawrence E Roebel	0491	AP30
Charles J Fisher	R-435	LFCP4	Saul H Rosenberg	0460	AP10
Bryan A Ford	R-4FA	AP9-1	Efraim Shek	R4R1	NCA4-4
Joseph M Fortunak	R453	NCR13-3	Brian B Spear	R-424	AP6A-1
Richard G Granneman	04CE	AP13A-3	Damien Springuel	R4BK	AP30
Jonathan Greer	046Y	AP10-2	Joseph Stauffer	096R	AP30
Don N Halbert	R4MD	AP10	Kenneth D Stiles	R404	AP9-1
Arthur A Hancock	D-4MN	AP9A-3	James Sullivan	R464	AP9A-3
Keith F Hendricks	06MT	AP34-3	James B Summers	R467	AP10
John Hofstetter	040H	AP4	Carol S Surowy	R-47W	AP9A-3
Steve King	041K	NCR13-4	James L Tyree	R441	AP34-3
Gayle A Kirkpatrick	R50A	AP34	Danhui Wang	R4BJ	AP30
William E Kohlbrenner	047D	AP52-1	Michael J Ward	0377	AP6D-2
Devalina Law	R4P3	AP9	Steven F Weinstock	0377	AP6D-2
Suzanne Lebold	R50A	AP34-3			

RE: A-429202, Candidate for the Treatment of Pain  
 Drug Development Candidate Meeting  
 Thursday, June 13, 2002  
 10:00 a.m. to 12:00 p.m.  
 AP10 3-West A & B

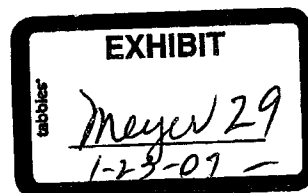
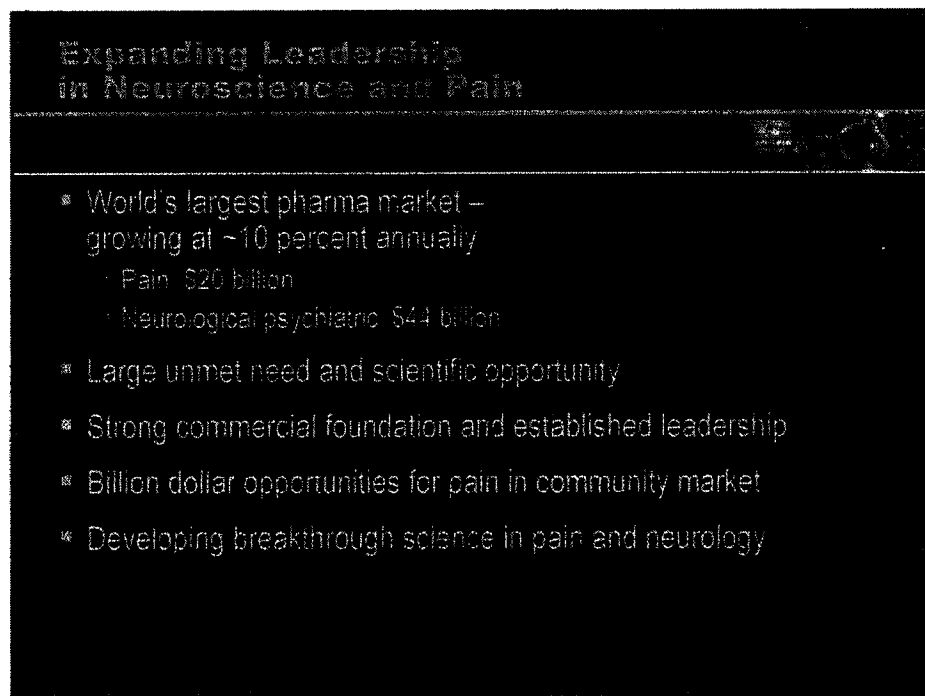
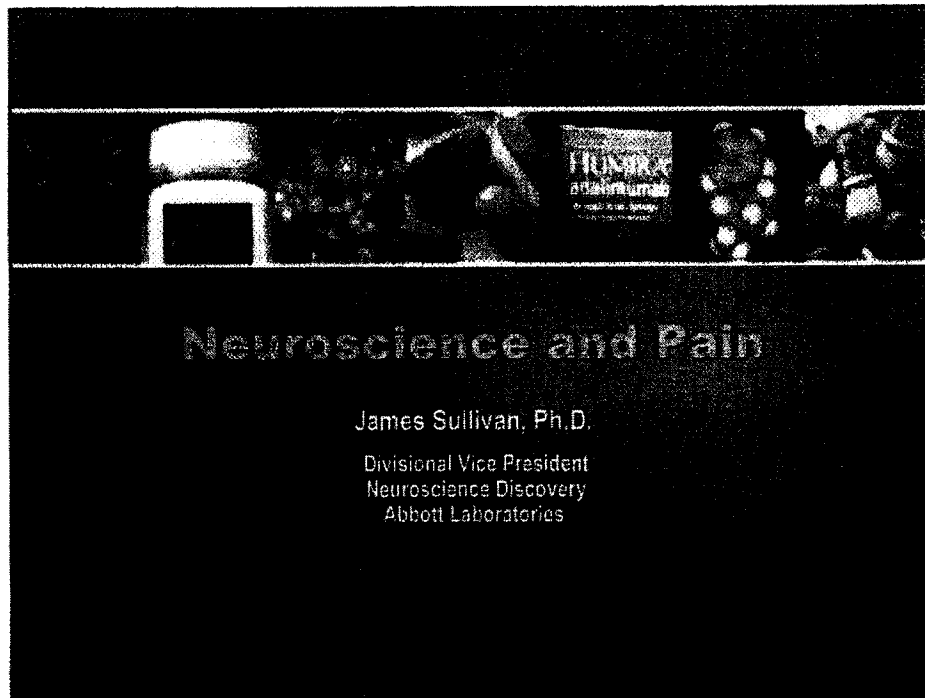
Please review the attached document and forward questions to me by e-mail or fax (7-9195) by June 7. We will address your questions during the DDC presentation on June 13.

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# **Meyer Deposition Exhibit 29**

**P's Exhibit DM**



## Established Leadership

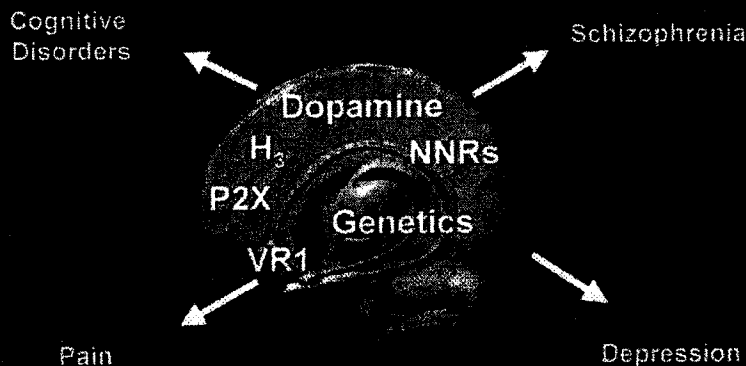
### STRONG FOUNDATION IN PAIN AND NEUROSCIENCE

- Major marketed products: \$1.5 billion in sales
  - Depakote: #1 treatment for bipolar and #1 branded treatment for epilepsy
  - Recognized brands in pain management (Vicodin, Dilaudid, Morphine)
- Resources to develop breakthrough science
  - 350 scientists
  - Centers of Excellence (Ludwigshafen, Abbott Park)
- Strategic collaborations augment internal programs
  - NeuroSearch, Idagen, Myriad



## Abbott's Leading-Edge R&D Strategy in Pain and Neuroscience

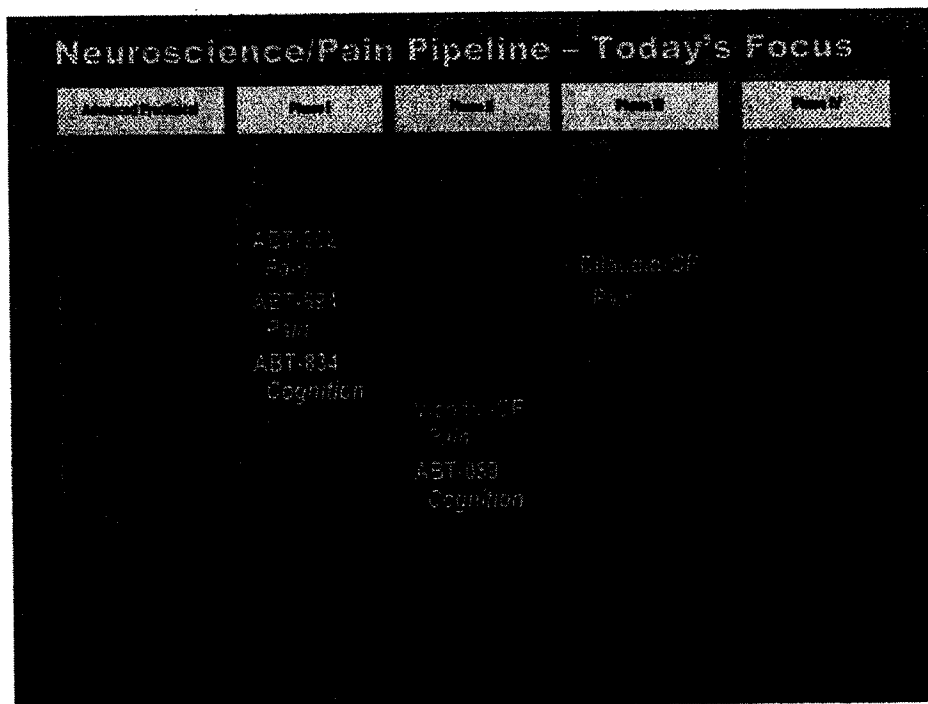
### LEVERAGING INNOVATIVE TECHNOLOGY PLATFORMS AND EXISTING BRAND EQUITY



Neuroscience/Pain Pipeline				
Compound/Indication	Phase I	Phase II	Phase III	Phase IV
	ABT-202			
	Pain			
ABT-769	ABT-694			
VR1	Pain			
Na channel	ABT-634			
D3 antagonist	Cognition			
H3 antagonist	ABT-239			
NMR	Cognition			
5HT5				
P2X				
D4 Agonist				

Neuroscience/Pain Pipeline				
Compound/Indication	Phase I	Phase II	Phase III	Phase IV
	ABT-202			Depakote-ER
	Pain			
ABT-769	ABT-694		Dilaudid-CR	
VR1	Pain		Pain	
Na channel	ABT-634			
D3 antagonist	Cognition			
H3 antagonist	ABT-239	Vicodin-CR		
NMR	Cognition	Pain		
5HT5		ABT-069		
P2X		Cognition		
D4 Agonist				

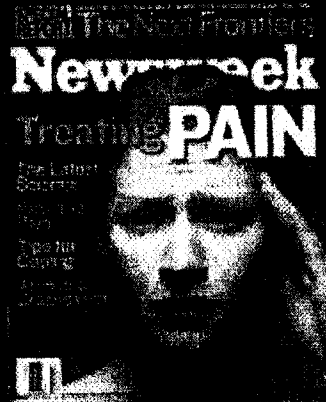




### The Pain Market

**PAIN – #1 REASON PATIENTS SEEK PHYSICIAN CARE**

- \$20 billion market worldwide – ~10 percent annual growth
- Vast, underserved patient population
- Need for more efficacious and better-tolerated drugs
  - No breakthrough classes of pain drugs in 30 years
  - Rapid advances in understanding of pain pathways have generated new molecular targets



The image shows the cover of a magazine titled 'Newweek'. The main headline is 'Treating PAIN'. Below the headline, there is a black and white photograph of a woman's face. To the left of the photo, there is a list of topics: 'The Latest Science', 'New Treatments', 'The Latest Science', 'New Treatments', 'The Latest Science', 'New Treatments'. At the bottom left of the cover, there is a small logo that looks like 'm'.

## Pain

### TWO MAJOR PAIN STATES

- \* Inflammatory/nociceptive pain
- \* Neuropathic pain

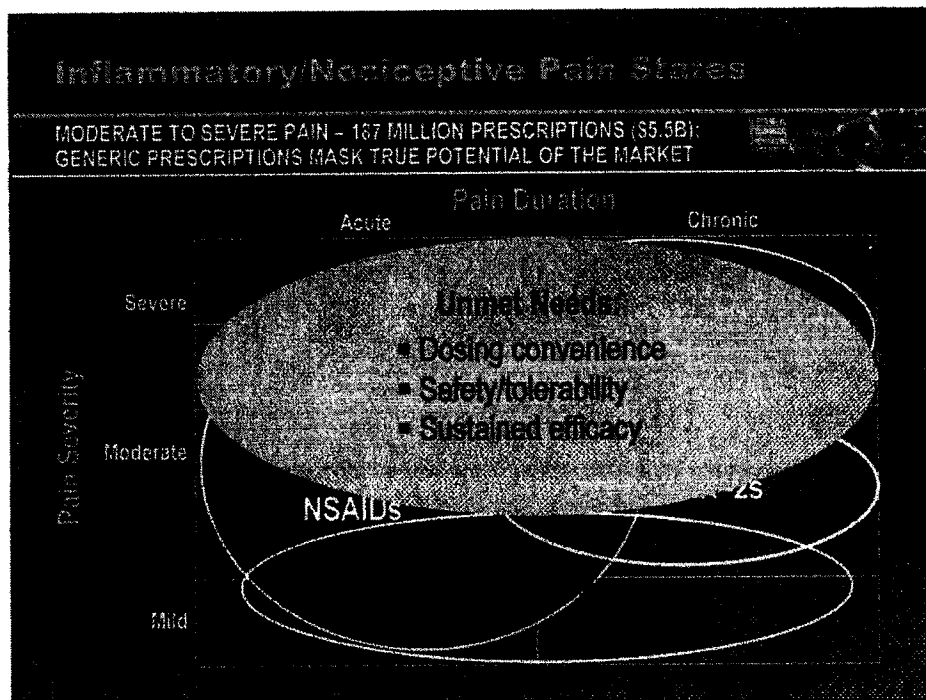
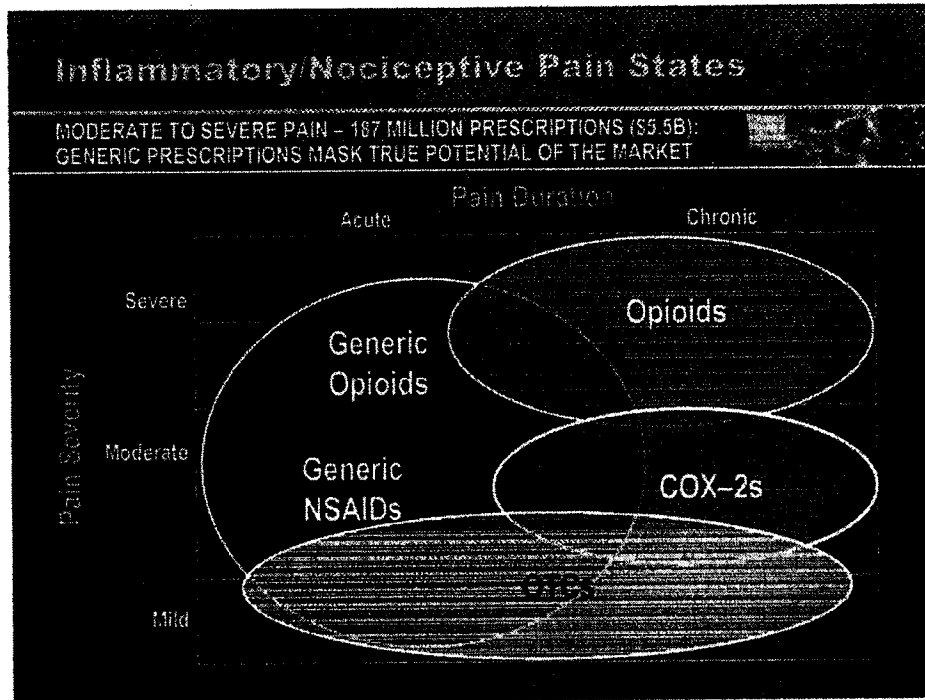


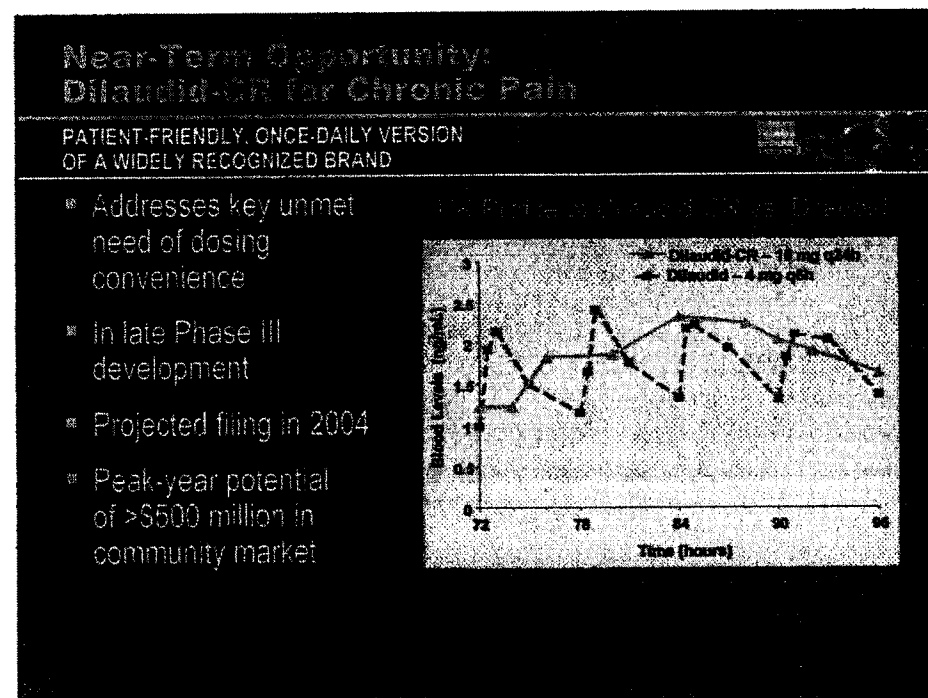
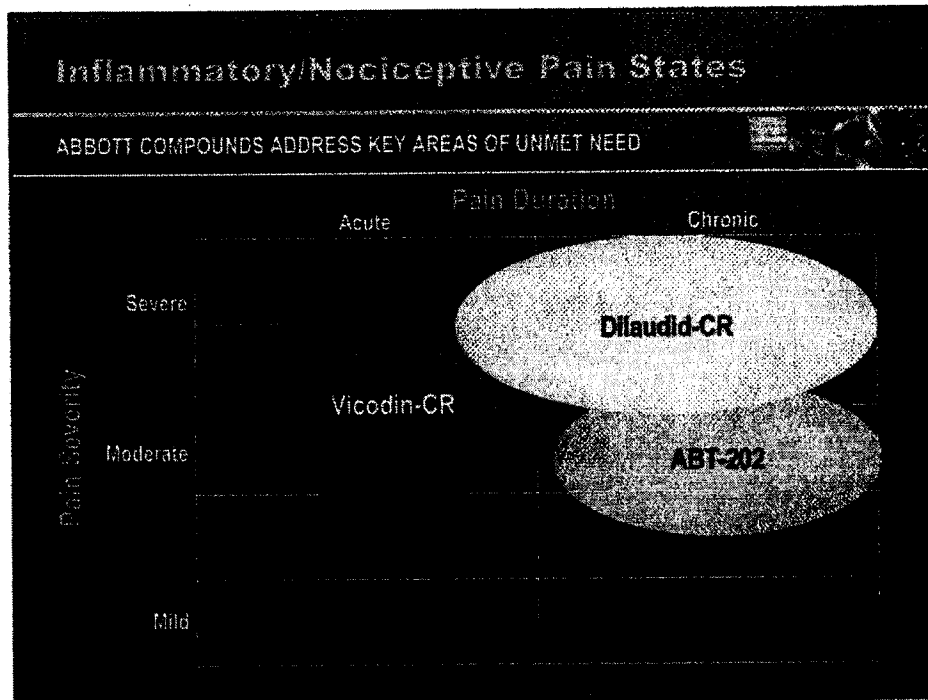
## Pain

### TWO MAJOR PAIN STATES

- \* Inflammatory/nociceptive pain
  - Acute – Post-op pain, bone fractures
  - Chronic – OA, RA, back pain, cancer pain





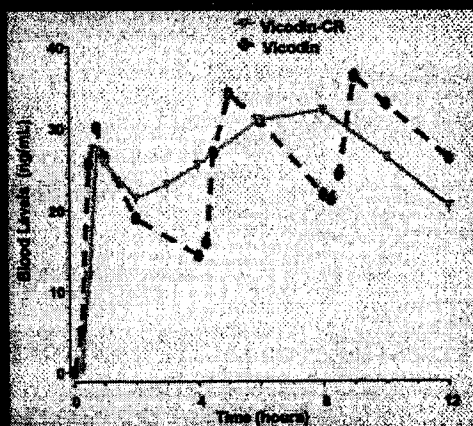


## Near-Term Opportunity: Vicodin-CR for Acute Pain

MORE CONVENIENT DOSING OF A WIDELY RECOGNIZED BRAND

- \* 8 – 12 hour dosing  
(vs. 3 – 4 hour dosing  
with current version)
- \* Rapid and sustained  
analgesia for acute pain
- \* Currently in Phase II
- \* Projected filing in 2005
- \* Peak-year potential  
of >\$500 million in  
community market

Pharmacokinetic Profile of Vicodin-CR vs. Vicodin



## Neuronal Nicotinic Acetylcholine Receptor (NNR)

BREAKTHROUGH TECHNOLOGY PLATFORM FOR PAIN / NEUROSCIENCE

- \* Abbott is the first company to establish efficacy of NNRs in:

Pain

ADHD

AD

ADHD

Alzheimer's Disease (AD)

Schizophrenia

NNR

Neuropathic Pain

Mild Cognitive  
Impairment

Inflammatory Pain

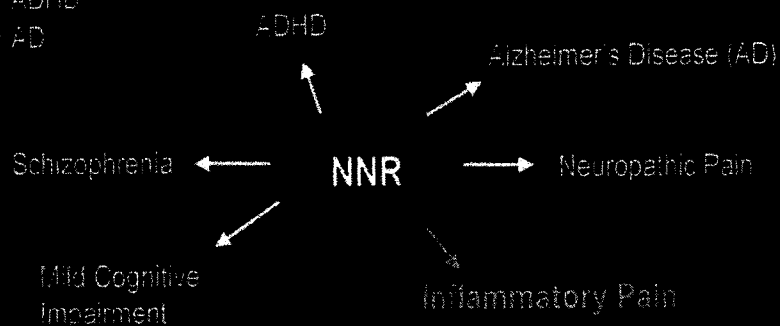


## Neuronal Nicotinic Acetylcholine Receptor (NNR)

BREAKTHROUGH TECHNOLOGY PLATFORM FOR PAIN / NEUROSCIENCE

- Abbott is the first company to establish efficacy of NNRs in:

- Pain
- ADHD
- AD



## ABT-202: NNR for Chronic Inflammatory/Nociceptive Pain

EARLY-STAGE DEVELOPMENT

- Superior efficacy vs. COX-2/NSAIDs
- Efficacy comparable to opioids in inflammatory pain models
- Tolerability very favorable vs. opioids

### Preclinical Efficacy – Inflammatory/Nociceptive Pain

	Mild to Moderate	Moderate to Severe
ABT-202	>75%	>75%
COX-2	>75%	<30%
Opioids	>75%	>75%

## Pain

### TWO MAJOR PAIN STATES

- Neuropathic pain – encompasses a wide range of pain syndromes
  - Diabetic neuropathy
  - Cancer neuropathy
  - HIV pain
  - Postherpetic neuralgia



## Neuropathic Pain

### GROWING MARKET WITH SIGNIFICANT UNMET MEDICAL NEEDS

- 10 million patients worldwide
- Current market leaders only offer modest efficacy
- Key needs:
  - Greater efficacy
  - Faster onset of action

Chronic  
Neuropathic

Unmet  
Need

Efficacy

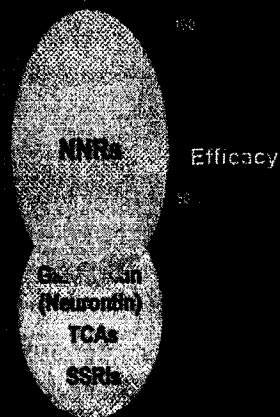
Gabapentin  
(Neurontin)  
TCAs  
SSRIs

## Neuropathic Pain

### ABBOTT COMPOUNDS ADDRESS UNMET NEEDS

- 10 million patients worldwide
- Current market leaders only offer modest efficacy
- Key needs:
  - Greater efficacy
  - Faster onset of action

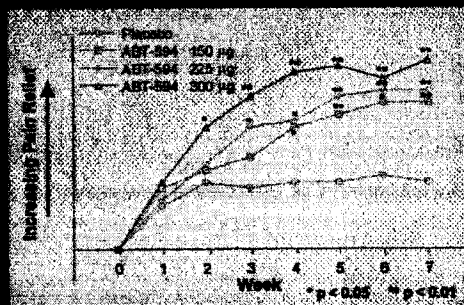
Chronic  
Neuropathic

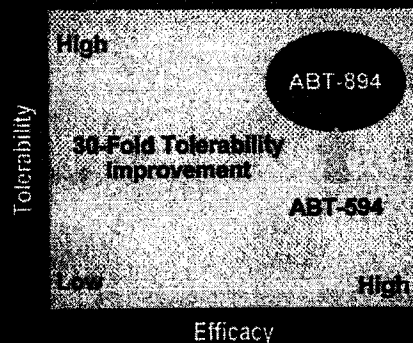


## ABT-594: First-Generation NNA

### EFFICACY IN MULTIPLE CLINICAL MODELS

- Efficacy comparable to market leader in neuropathic pain
- Limited tolerability
  - Key Issue: nausea and GI side effects
- Discovery goal: Identify compound with 30-fold improvement in therapeutic index



**ABT-594: First-Generation NNR****EFFICACY IN MULTIPLE CLINICAL MODELS**

- Next-generation compound: ABT-894

**ABT-894: Next-Generation NNR****EARLY-STAGE DEVELOPMENT FOR NEUROPATHIC PAIN**

- Full efficacy in multiple preclinical models of neuropathic pain

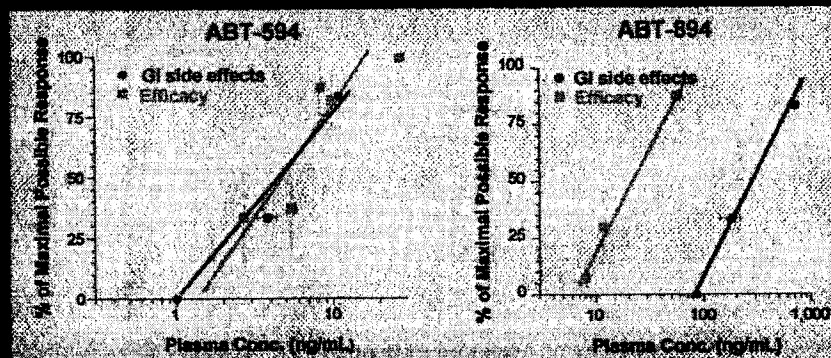
**Preclinical Efficacy – Neuropathic Pain**

	Scholar's Nerve Injury	Chemotherapy
ABT-894	>75%	>75%
COX-2	<30%	<30%
Gabapentin (Neurontin)	>75%	50%

## ABT-894: Next-Generation NNR

### FULL EFFICACY WITHOUT GI SIDE EFFECTS

- \* Exhibits marked improvement vs. ABT-594 in models of neuropathic pain

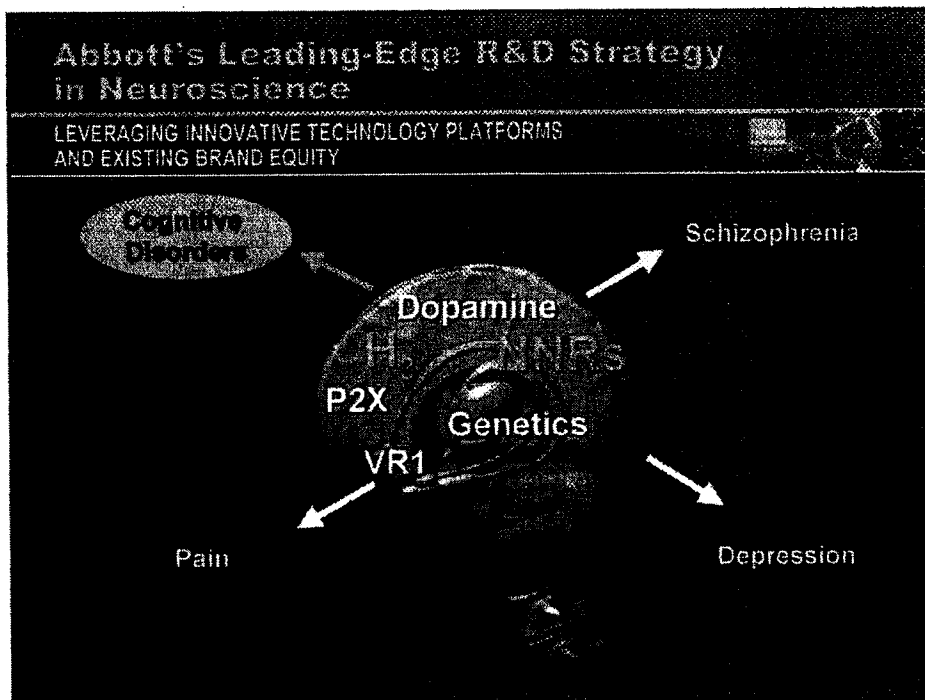


## Abbott is Poised to Expand its Presence in Pain

### SIGNIFICANT NEAR-TERM AND LONG-TERM OPPORTUNITY

- \* Today
  - Widely recognized brand names in pain (Vicodin, Dilaudid, Morphine)
- \* Future
  - Potential for combined sales of >\$1 billion in community market
    - Dilaudid-CR: projected 2004 filing
    - Vicodin-CR: projected 2006 filing
  - Long-term potential to revolutionize pain treatment
    - 2008 - 2010: ABT-262 and ABT-894

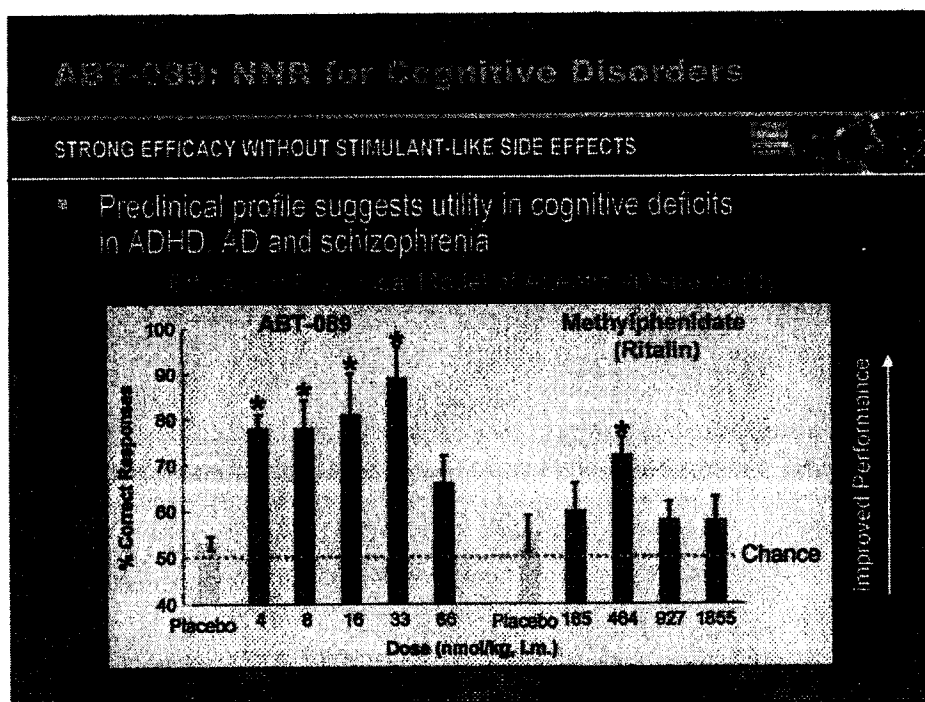
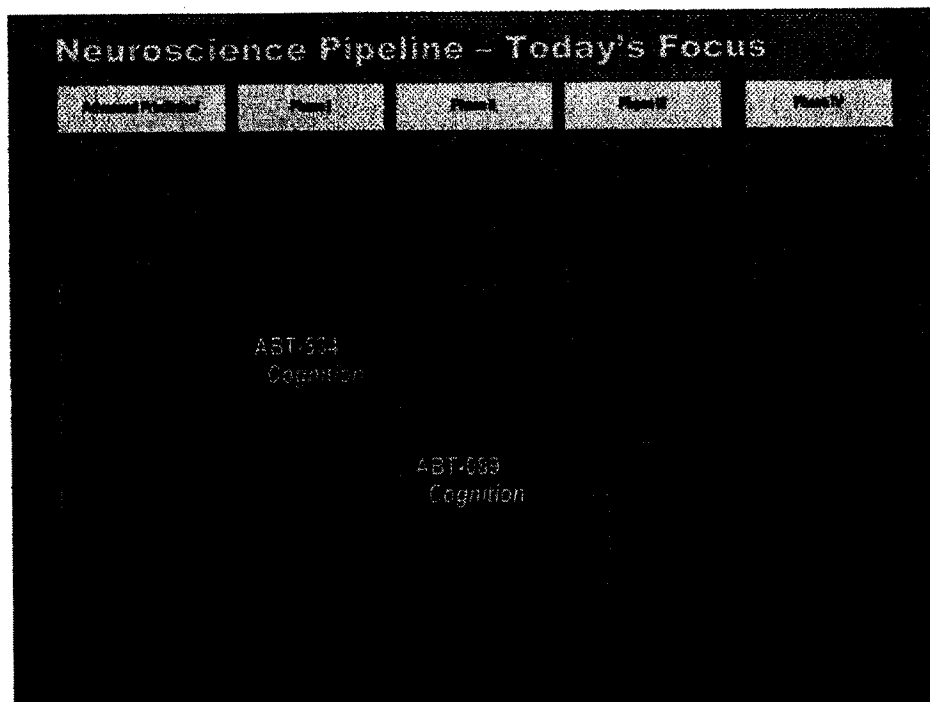




**Cognitive Disorders**

- \* ADHD, mild cognitive impairment, schizophrenia, and Alzheimer's disease affect greater than 35 million worldwide
- \* Current therapies
  - Weak efficacy in Alzheimer's disease
  - No treatments available for cognitive aspects of schizophrenia
  - Stimulants used to treat ADHD

A black and white silhouette of a person's head and shoulders, facing right, positioned on the right side of the slide.



## ABT-089: NNR for Cognitive Disorders

- \* Excellent safety profile in preclinical models

>100-fold separation between efficacy and GI side effects

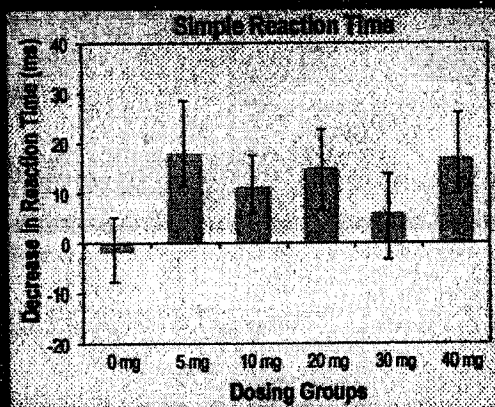


## ABT-089: Next-Generation NNR

### PHASE I DATA SUPPORTS PRECLINICAL PROFILE

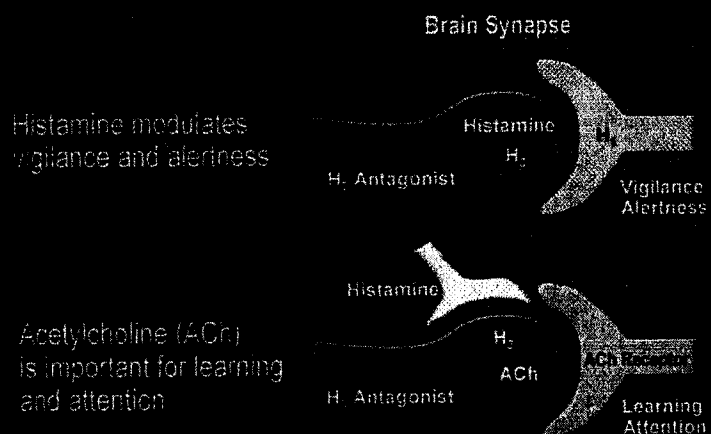
- \* Phase I completed
  - Efficacy signal
  - Very well-tolerated
- \* Phase II underway
  - Efficacy studies
    - AD
    - ADHD
    - Schizophrenia

Improvement in Memory of Wisconsin Patients



## Histamine H<sub>2</sub> Receptors

### NEW MOLECULAR APPROACH TO ATTENTIONAL/COGNITIVE DISORDERS



## Novel H<sub>2</sub> Receptor Antagonists Identified

- \* Designed by molecular modeling (structural biology)
- \* Potent and selective antagonists identified
- \* Lead compounds active in preclinical models of attention/cognition

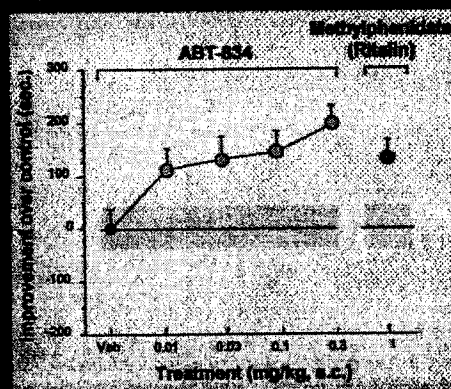
Interaction of Abbott Compound With Human H<sub>2</sub> Receptors

## H<sub>3</sub> Antagonists for Cognitive Disorders

### ABT-834 - EARLY CLINICAL DEVELOPMENT

- Potent and selective H<sub>3</sub> antagonist
- Efficacy in attention/cognition models
- Excellent safety and tolerability
  - No stimulant liability unlike stimulants
- Very favorable PK
  - No drug-drug interactions unlike atomoxetine (Strattera)

Robust Model of Attention Hyperactivity



## Expanding Leadership in Neuroscience and Pain

- World's largest pharma market – growing at ~10 percent annually
  - Pain: \$20 billion
  - Neurological/psychiatric: \$44 billion
- Large unmet need and scientific opportunity
- Strong commercial foundation and established leadership
- Billion dollar opportunities for pain in community market
- Developing breakthrough science in pain and neurology



